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Preface

There are new perspectives in the treatment of intra-articular complications of haemophilia that I have tried to clarify in this book with the help of clinicians and academics who have a high degree of expertise in the field. The patient with haemophilia presents a particular challenge for those providing musculoskeletal care. Haemophilia is a lifelong inherited bleeding disorder characterized by spontaneous bleeding resulting in painful joint deformities.

Unfortunately 70% of those with haemophilia worldwide have no access to adequate haematological care. Many of those individuals are untreated, and therefore suffer enormously. Often, expert orthopaedic care cannot be provided to the haemophilia patient because of the constraint of lack of clotting factor provision for economic reasons.

In the so-called ‘developed world’, the availability of safe and effective clotting factor concentrate has enabled the orthopaedic surgeon to approach the patient with haemophilia with almost the same security as a patient without a bleeding disorder. The development of high-purity concentrates has enabled peri-operative delivery of clotting factor by continuous infusion, giving added safety during the period of surgery and the possibility of more intensive physiotherapy and rehabilitation postoperatively. The newer recombinant clotting factor concentrates are particularly easy to deliver by continuous infusion.

Today, synoviortheses, synovectomies, joint debridements, tendon lengthenings, osteotomies, joint fusions, removals of osteophytes and haemophilic cysts, joint arthroplasties and other orthopaedic procedures can be performed to relieve pain. Furthermore, these procedures are now available for the patient with an inhibitor (alloantibodies against infused exogenous factor VIII or IX).

I have tried to provide an in-depth analysis of the new perspectives involved in the treatment of those with haemophilia, and I hope that this book will provide information that will be helpful for those treating the articular manifestations of haemophilia. My experience as Editor of this book has been rewarding and challenging. I am indebted to my colleagues who have contributed chapters.

Editor: E.C. Rodriguez-Merchan
PART 1

General principles
Introduction

The management of orthopaedic problems in haemophiliacs requires a haematologist, whose function is to control haemostasis, an orthopaedist, physical therapist, orthotist and occupational therapist, all of whom concentrate on the preservation and restoration of function to the musculoskeletal system. The clinical severity of haemophilia is usually related to the plasma level of factor VIII or factor IX. Patients are classified as having mild, moderate or severe haemophilia depending on the level of the deficient factor, which can be > 5% of normal in mild cases and < 1% of normal in severe haemophilia. This is reflected in the frequency and causes of bleeding. Whereas a patient with mild haemophilia will bleed rarely, usually only after significant trauma or surgery, those with severe haemophilia may have several episodes per month, and typically bleed spontaneously as a result of minimal trauma or activities of daily living. Over 90% of bleeding episodes in haemophilic patients occur within the musculoskeletal system and, of these, 80% occur within the joints.

Management of intra-articular bleeds

The vast majority of bleeding episodes in haemophiliacs occur within the joints (haemarthrosis). Of these haemorrhages, the ankles, elbows and knees account for almost 80%. The involved articulation is usually held in flexion, and active and passive motion is painful and very restricted. With the early provision of the missing coagulation factor, haemorrhages can be controlled and conservative orthopaedic management can usually terminate the episode without any long-term complications.

Should the haemorrhage persist or a re-bleed occur, the synovium begins to hypertrophy (Fig. 1.1) and a vicious circle of chronic synovitis develops, leading to joint destruction and classical osteoarthritis. The hypertrophic synovium is characterized by villous formation, markedly increased vascularity and the chronic presence of inflammatory cells. Synovitis causes hypertrophy of the epiphyseal growth plates [1].

Bone hypertrophy may lead to leg length discrepancies, angular deformities and alterations of contour in the developing skeleton.

If the synovitis is not controlled, cartilage damage will follow. The synoviocytes disintegrate and release lysosomal enzymes, which not only destroy articular cartilage but also further inflame the synovial tissue. Blood breakdown products also affect the chondrocytes. The haemosiderin staining of the synovium and cartilage bears testimony to the destructive elements of proteolytic enzymes. Symptoms of chronic arthropathy typically develop by the second or third decade. As the joint cartilage progressively degrades, deterioration in joint function occurs.

Continuous prophylactic clotting factor replacement (prophylactic therapy)

Prophylactic therapy has been reported to slow the natural course of haemophilic arthropathy. Swedish authors were the first to report that continuous prophylaxis from ages 2 to 18 years prevented the development of haemophilic arthropathy if
the concentration of the patient's deficient factor was prevented from falling below 1% of normal [2]. This can be achieved with administration of 25–40 units/kg factor VIII three times weekly in patients with haemophilia A and 25–40 units/kg factor IX twice weekly in patients with haemophilia B.

Management of haemarthroses

If prophylactic therapy is not feasible because of expense or lack of venous access, then a major haemarthrosis must be aggressively treated to prevent progression to synovitis, recurrent joint bleeds and, ultimately, end-stage arthritis. These joint bleeds need the following:
1. transfusion to 50%;
2. aspiration (arthrocentesis) to debulk the joint blood;
3. short-term splinting for 48 h; and
4. transfusion every 48 h until the joint is fully rehabilitated and there is no evidence of synovitis. This requires 10–30 days of transfusion.

Management of synovitis

If left untreated, synovitis followed by degenerative changes within the joint will occur and a stiff or painful joint will result. Both surgical synovectomy and radioactive synoviorthesis are procedures for synovial destruction used in a number of haemophilia centres for the management of chronic haemophilic synovitis. Taking into account the risk of infection after surgical procedures in human immunodeficiency virus (HIV) positive patients, synoviorthesis is recommended first. Radioactive synoviorthesis is also of particular interest in patients with haemophilia caused by factor inhibitors, who otherwise are difficult to treat. No complication related to radiation synovectomy has been reported to date. For the treatment of chronic haemophilic synovitis, synoviorthesis should always be indicated as the first procedure. It is an easy procedure with a number of satisfactory results [3].

With $^{198}$Au synoviorthesis there is an expected 75% success rate, while with $^{90}$Y synoviorthesis there is an expected 85% or more success rate. It is important to emphasize that no more than three synoviortheses can be repeated with a 3-month interval between them. If, after three procedures, synoviorthesis fails, a surgical synovectomy is indicated. Rifampicin is expected to produce similar results to $^{90}$Y in the small joints (elbows and ankles), but several weekly, painful injections are needed; in addition, rifampicin synoviorthesis is not recommended for the knee joint. Surgical synovectomy generally achieves similar results to $^{90}$Y synoviorthesis; however, as it is a surgical procedure under general anaesthesia, it is accompanied by a certain number of complications common to surgical procedures.

When surgical synovectomy is indicated for the knee, arthroscopic synovectomy is recommended because of the lower risk of infection and lack of postoperative mobility; however, there are no true comparative studies to conclude which type of synovectomy is most efficient. For the elbows and ankles, open surgical synovectomy is advised. It is possible that the way forward is to use radioactive synoviorthesis ($^{90}$Y or $^{32}$P) first, and then up to three times. If this fails for the knee, then arthroscopic synovectomy is indicated. Open surgical synovectomy for the knee should be the method of last resort, after three previous failures with the other procedures. Although difficulties arise when comparing different studies regarding synovitis of the knee, the decreased frequency of haemarthrosis after synoviorthesis is not as great as after operative synovectomy.

From the point of view of quality of life and economy, radioactive synoviorthesis offers advantages in that it is usually almost painless and requires minimum replacement therapy. Open surgical synovectomy of the knee in haemophilic patients who are managed with conventional postoperative therapy has frequently been complicated by a loss of motion, even with prolonged inpatient treatment. Rehabilitation after synovectomy of the knee is particularly difficult for children with haemophilia because they tend to be less motivated and co-operate less with the postoperative physical therapy programme. The rationale behind arthroscopic synovectomy of the knee in haemophilia is to provide a similar decrease in bleeding episodes as open synovectomy, while avoiding the loss of range of motion that can occur.

Personal experience and the general recommendation among orthopaedic surgeons and haematologists is that when three early consecutive synoviortheses (repeated every 3 months) fail to halt synovitis, a surgical synovectomy (open or by arthroscopy) should be immediately considered. Although patients are admitted to hospital for synoviorthesis for haematological preparation, it must be recognized that it is not necessary in every case and the procedure could be performed at the outpatient clinic with minimal risks. Radioactive synoviorthesis should be performed in very young patients, when the amount of synovial membrane is still moderate. Once the degree of synovitis has become severe, the expected results of synoviorthesis are decreased.

Management of flexion contractures (tendon lengthening, extension osteotomy and external fixators)

In those patients with flexion contractures of the knee or ankle, provided the joints are preserved (without haemophilic arthropathy), it is advisable to carry out a tendon lengthening procedure in order to obtain adequate joint extension and to improve articular function. The most frequent tendon lengthening classically performed on haemophiliacs are Z-lengthening of the Achilles tendon (to correct equinus of the foot) and the so-called hamstrings release (commonly associated with a posterior capsulotomy) for flexion contractures of the knee.

At the knee, extension supracondylar osteotomy can be used to correct a fixed-knee flexion contracture. It is a major procedure which requires fracturing the femur at its supracondylar
Joint débridement

Joint débridement is commonly performed on young patients with severe haemophilic arthropathy of the knee, in patients who the orthopaedic surgeon in charge considers are too young to indicate a total joint replacement. In other words, débridement is a procedure that can alleviate articular pain and bleeding for a number of years and delays the need for a total joint arthroplasty. Joint débridement consists of opening the joint in order to remove existing osteophytes, resect the synovium and carry out curettage of the articular cartilage of femoral condyles, tibial plateaus and patella.

Some authors do not believe in the efficacy of débridement and so when facing a severe degree of arthropathy in a young patient they directly indicate a total knee replacement. It should be emphasized that if débridement fails, a joint arthroplasty can be performed by the same approach. Some authors perform joint débridement by arthroscopic means with similar results to open surgery. Often, a synovectomy and débridement are performed together because haemophilic synovitis and early arthropathy commonly coexist. Again, postoperative rehabilitation is paramount to avoid loss of range of motion, and therefore should be associated with adequate haematological control in order to avoid re-bleedings.

Realignment osteotomy

Sometimes, during childhood, adolescence or early adulthood, haemophilic joints undergo an alteration of their normal axis. Knees show varus, valgus and flexion deformities, and something similar may occur at the ankle joint. When the malaligned joint is painful, the patient needs an alignment osteotomy. The most common osteotomies performed in haemophiliacs are: proximal tibial valgus osteotomy, supracondylar femoral varus osteotomy, ankle alignment osteotomy and knee extension osteotomy.

In all of these the rationale is to produce a fracture at an adequate place in order to re-align the joint to a normal axis. After the osteotomy it is necessary to obtain an adequate bone fixation by any kind of internal fixation device. (I have sometimes corrected a flexion contracture of the knee at the same time as a spontaneous supracondylar fracture of the femur.) When axial malalignment occurs in a joint with severe haemophilic arthropathy, a total joint arthroplasty is usually indicated and hence both problems can be solved at the same time.

Arthrodesis

Joint fusion (arthrodesis) is today used only at the ankle. It is indicated when a severe ankle arthropathy causes intense pain and/or disability, ankle arthroplasty being the alternative. However, ankle replacement has not been proved to be better than arthrodesis (not only in haemophiliacs). Ankle arthrodesis usually requires two approaches in order to remove the involved cartilaginous surfaces of distal tibia and talus. Then it is necessary to compress the surfaces using lag screws, staples or an external fixator. By 10–12 weeks joint fusion is usually achieved and hence all immobilization devices can be removed. Ankle pain is likely to disappear although subtalar pain sometimes appears after arthrodesis. Such pain is a result of the abnormal biomechanics of the foot after ankle fusion. In summary, ankle arthrodesis is an extreme surgical procedure which considerably improves joint pain but sometimes provokes another type of pain, usually not so intense as the primary one.
Joint prosthesis
The most common total joint replacements performed in adult haemophilic patients are at the hip and at the knee, and they are indicated when pain and disability are intense. Hip arthropathy causes pain at the groin which can irradiate to the ipsilateral knee. Sometimes it is advisable to perform two or three surgical procedures in a single surgical session in order to maximize the whole function of the affected limbs. Alternatively, it is possible to operate on the most painful joint first and then treat the others (3–6 months later). Shoulder and elbow arthroplasties have been rarely used in haemophilia because their results have not been as successful as those obtained in hips and knees.

Total knee replacement
Most total knee arthroplasties (TKAs) are versions of a total condylar arthroplasty. The surgical procedure is commonly performed under ischaemia through a straight anterior incision and a parapatellar medial approach. It is carried out with the help of intra- and extramedullary guides, which facilitate adequate bone cuts on distal femur and proximal tibia; these cuts are needed for the implantation of the prosthetic components, using bone cement. Both cruciate ligaments (anterior and posterior) are usually removed during the operation. After the implantation of the prosthesis, the tourniquet is released in order to carry out meticulous haemostasis. The results obtained with TKA in haemophilia are quite satisfactory so far, which is why a prosthesis is considered to be a good procedure in severe cases of knee haemophilic arthropathy (Fig. 1.2).

Total hip replacement
Although there are a number of prosthetic models (cemented and cementless), the most commonly used is Charnley’s cemented low-friction arthroplasty. The indications for a total hip arthroplasty are intense groin pain (sometimes irradiating...
to the ipsilateral knee) associated with advanced haemophilic arthropathy. There are a number of surgical approaches, but the most commonly used are the lateral and the posterior approaches. During the surgical procedure the acetabulum has to be reamed before the implantation of the acetabular component, the femoral head has to be removed and the femoral canal prepared for the implantation of the femoral stem. Published results have been highly satisfactory in haemophilia.

**Anatomical considerations**

**Shoulder arthropathy**

Growth disturbance of the epiphysis may cause a small atrophic humeral head with a varus deformity. In the mature shoulder, osteophyte formation may be pronounced. Arthrodesis of the shoulder has proved to be a good and reliable procedure. However, in haemophiliacs, where elbow joint destruction and limitation of movement are common, this procedure must be more critically reviewed. Total joint arthroplasty remains controversial.

**Elbow arthropathy**

Because of the severe valgus deformity that many haemophilic patients have at the elbow, the ulnar nerve can be overstretched. Such a problem is usually detected early because of the typical paraesthesias that are encountered at the fourth and fifth fingers. Diagnosis is confirmed by means of an electromyogram (EMG), which defines whether the involvement is a neurapraxia, neurotmesis or axonotmesis: that is to say, whether the involvement is reversible, partially reversible or irreversible, respectively. The surgical procedure consists of the release of the ulnar nerve from the sulcus where it normally runs (neurolysis). It is a relatively simple procedure with a high rate of satisfactory results, provided that the lesion is reversible.

Ishiguro *et al.* [4] investigated the characteristics of haemophilic arthropathy of the elbow joint in 32 patients aged 5–12 years.
who had been followed from infancy. There was a discrepancy between the growth of the intra-articular subchondral epiphysial cartilage and the cartilage of the medial and lateral epicondyles (apophyseal cartilage). This differential growth may be an important factor in the development of complicated and variable haemophilic elbow deformities. As this joint may prove to be problematic, the surgical options are greatly reduced.

Excision of the radial head and partial open synovectomy is a consistently reliable operation, which appears to prolong the functional life of the elbow joint. With proper selection it dramatically reduces the rate of haemarthroses, improves forearm pronation-supination by 20–60°, decreases pain, improves function and does not cause elbow instability. The use of total elbow joint replacement is not yet an accepted form of therapy, and so two options remain: the use of an orthotic brace or arthrodesis.

**Hip arthropathy**

Fortunately, bleeds into the hip joint are uncommon. However, they carry the added risk of developing avascular necrosis. Haemorrhages in the growing hip may result in changes similar to Perthes' disease. To reduce the risk of avascular necrosis, these patients should have the hip joint aspirated. End-stage haemophilic arthropathy necessitating arthroplasty is infrequent in the hip. Although results are inferior to those obtained in arthrosis, total hip replacement should be considered in haemophilias. Kelley *et al.* [5] reported a high rate of loosening of cemented hip prostheses in patients with haemophilia. There was also a high overall rate of mortality and a high rate of late deep infection in patients who were seropositive for HIV.

**Knee arthropathy**

Smith *et al.* [6] proposed that angular deformities in the lower limbs placed a varus or valgus strain on the knee joint, and that this malalignment was the trigger for haemarthroses. Based upon this theory, osteotomies were carried out on the long bones. Arthrodesis of a knee joint is a relatively simple procedure, but haemarthrosis is a systemic disorder and not just a regional knee pathology. Therefore, one must take into account that the ankle joint distal to the arthrodesed knee or the hip proximal to that knee may become equally pathological, and a double arthrodesis in the same limb makes ambulation extremely difficult. However, total joint replacements in relatively young patients hold intrinsic dangers of prosthesis loosening and late joint infections in immunologically compromised persons. Débridement should be considered in the young haemophilic to avoid or delay TKA. The operation may give the patient years of life without pain.

The primary goals of TKA are to relieve pain, restore function and achieve stability. In chronic haemophilic arthropathy the operation is technically demanding because of soft-tissue fibrosis, flexion contractures and poor quality of the bone. For these reasons, complications other than infection in HIV-negative haemophilia are more prevalent than in osteoarthritis. Moreover, if the patient is HIV-positive with a CD4 count of < 200/mm³, the risk of postoperative infection after TKA can reach up to 30%.

In the era of total joint replacement, a TKA should be indicated in HIV-positive patients with haemophilia who have severe pain in the knee and disability. However, the high risk of infection and other postoperative complications is a concern. It should not be inferred that a TKA should be avoided in a HIV-positive patient with haemophilia, but that the orthopaedic surgeon should weigh the risks and benefits. A careful and conservative approach is needed. However, recent improvements in medical treatment can diminish the previously reported rate of postoperative infection and give grounds for continued optimism.

**Ankle arthropathy**

The most common deformities associated with ankle and subtalar arthropathy are fixed plantar flexion, usually as a result of anterior changes; varus hindfoot, which suggests subtalar involvement; and valgus at the ankle. The non-operative management of ankle arthropathy includes splints, support shoes or boots, wedge insoles and calipers. Supramalleolar varus osteotomy has been reported for haemophilic arthropathy and secondary valgus deformity. The procedure is an attractive alternative to the more commonly used surgical option of arthrodesis [7].

**Management of intra-muscular bleeds**

In the majority of cases, bleeds within muscles are caused by trauma. They are very often associated with direct trauma and the pathology becomes quite evident because of the swelling, pain, local warmth and bruising that typically appear in the overlying skin. The vast majority of these muscle bleeds resolve spontaneously, leaving no functional loss. However, it is necessary to examine the patient carefully to ensure that there is no danger to vascular elements or neural compromise.

The muscles in the forearm and the shin are enclosed in tight fascial compartments, and even relatively small bleeds can cause a large rise in pressure in the intracompartmental space. Volkmann’s contracture of the hand and foot have been reported as a result of such bleeding incidences within the closed compartments. The treatment may be of a conservative nature wherein haemostasis is established, the limb rested in elevation, analgesia provided and, as the swelling subsides, there is a decrease in pain and a gradual return to function. Should the pressure be very high, decompression is vital. This decompression may be effected either by drainage of the haematoma or by formal surgery and incision of the fascial envelope. The most common and most serious of muscle bleeds occur in the iliopsoas muscle. Lower quadrant abdominal pain can mimic the symptomatology of an acute appendicitis. Compression of the femoral nerve may present as an area of reduced
sensation in the anterior aspect of the thigh. Attempts to extend the hip joint cause severe pain and force the patient into hyperlordosis of the lumbar spine.

As it is difficult clinically to differentiate between a bleed into the iliopoas muscle and an intra-articular haemorrhage into the hip joint, one must rely on objective testing. Ultrasound can differentiate between the largely extended joint capsule with intra-articular haemorrhage and the bleed that is situated within the muscle fibres. The iliopoas bleed takes a long time to improve, and the flexion contracture of the hip joint may persist for weeks. Secondary haemorrhages into the same area are common and so prophylactic factor replacement is advised. Whereas coxaemarthrosis is a problem costing days of extra treatment, an iliopoas haematoma may require weeks until full recovery is achieved.

Management of haemophilic cysts

The haemophilic cyst (pseudotumour) is basically an encapsulated haematoma. A thick fibrous capsule surrounds a haematoma in varying degrees of organization; calcification and ossification may be seen within it. Proximal haemophilic cysts occur in the proximal skeleton, especially around the femur and pelvis. They appear to originate in the soft tissue, erode bone secondarily from outside and develop slowly over many years. Haemophilic cysts occur in adults and do not respond to conservative treatment. Large proximal cysts in adults should be removed surgically as soon as they are diagnosed. Cysts occurring distal to the wrist and ankle appear to be secondary to intraosseous haemorrhage and develop rapidly. They are seen mainly in children and adolescents. Distal haemophilic cysts should be treated primarily with long-term replacement therapy and cast immobilization. In children, surgical removal or even amputation is indicated when conservative management fails to prevent progression. Percutaneous evacuation should be considered in inoperable advanced haemophilic cysts. Evacuation is carried out with a large trocar under image intensifier control; the cavity is filled with different quantities of fibrin seal or cancellous bone, depending on the size of the cyst.

The management of the patient with a haemophilic cyst is complex and with a high rate of potential complications. There are a number of therapeutic alternatives for this dangerous condition: embolization, radiation, percutaneous management, surgical removal and exeresis and filling of the dead cavity. It is hoped that with the advent of widespread maintenance therapy, haemophilic cysts will be less common in the future. It is important that they are diagnosed early, and prevention of muscular haematomas is key to reducing their incidence. Untreated, proximal haemophilic cysts will ultimately destroy soft tissues, erode bone and may produce neurovascular complications. Surgical excision is the treatment of choice but should only be carried out in major haemophilia centres by a multidisciplinary surgical team [8].

Management of fractures in haemophiliacs

The goal of modern fracture treatment is to obtain an optimal outcome with the patient’s return to full activity as soon as possible. Today, internal stabilization is indicated in most displaced fractures in the adult, whereas external fixation remains the best choice for initial stabilization with severe soft-tissue injuries. If a fracture is correctly treated in a haemophilic patient it will progress to consolidation in a similar time frame to those occurring in the general population [9].

The incidence of fracture in patients with haemophilia is controversial but, in our experience, it is infrequent because, understanding the gravity of their illness, these individuals are less ambulant so their daily activities are reduced because of associated arthropathy and contractures. However, poor musculature, osteoporosis and haemophilic changes in the bone may predispose them to risk of fractures. In patients with haemophilia fracture can occur after a trivial trauma, especially if associated factors of haemophilic arthropathy, muscle wasting and osteoporosis render the bone more fragile and prone to fracture. The bone may have structural changes secondary to subperiosteal or intraosseous bleeding producing haemophilic cysts.

Fractures can occur anywhere in the long bones but are more prevalent near the joints or in the diaphysis of the long bones. The lower limb bones, and especially the femur, are the most common site of fracture. Clinically, the symptoms of fractures are no different from those of non-haemophiliacs but the haematomas tend to be large in volume and may be the cause of acute compartment syndrome. Compartment syndrome is a condition characterized by raised pressure within a closed space with the potential to cause irreversible damage to the contents of the closed space. The surgeon must have a thorough knowledge of the surgical anatomy of the upper and lower extremities to perform adequate decompression under emergency conditions. If early treatment is better than late treatment, prevention must be better still. The only effective way to decompress an acute compartment syndrome is by surgical fasciotomy.

Risks of operating on an HIV-positive haemophilic patient

Haemophilic patients infected by the HIV virus are at risk of bacterial and opportunistic infection because of worsening immunodepression. In these patients, the risk of infection after orthopaedic surgery is of considerable concern [10]. A survey of haemophilia treatment centres in the USA by Ragni et al. [11] determined the incidence of postoperative infection in HIV-positive haemophilic patients with CD4 counts of 200/mm² or less. Of 66 patients undergoing 74 orthopaedic procedures, postoperative infection occurred in 10 patients (13%) up to 5 months postoperatively. Staphylococcus aureus was the most common organism (60%), and the knee was the most
commonly affected joint (90%). Arthroplasty appeared to have 10 times the risk of infection than other procedures. The risk of late infection of a total joint arthroplasty is higher, but when a patient is suffering incapacitating pain, the resulting improvement in their quality of life certainly warrants the procedure, provided the patient is fully informed about the surgery and its risks [12,13].

Orthopaedic surgery in haemophilic patients with inhibitors

The development of an inhibitor against factor VIII or factor IX is the most common and most serious complication of replacement therapy in patients with haemophilia A or B, resulting from the exclusive use of virus-inactivated plasma-derived concentrates or recombinant products. When present, the inhibitor inactivates the biological activity of infused factor VIII or factor IX, making the patient refractory to treatment. Between 10 and 30% of patients with severe haemophilia A, and 2–5% of patients with severe haemophilia B or mild/moderate haemophilia A, develop an inhibitor against factor VIII or factor IX after treatment with either plasma-derived or recombinant products. Inhibitor detection using the Bethesda assay, measured in Bethesda units (BU), is part of the regular follow-up for all haemophilic patients treated with such products. After the development of the inhibitor, the inhibitor titre decreases if no factor VIII- or factor IX-containing products are used for a long period so that the inhibitor may become undetectable. However, the inhibitor usually reappears after a new challenge with factor VIII- or factor IX-containing products (anamnestic response).

The author’s experience and a review of the literature on inhibitors have shown that, with the availability of FEIBA® and recombinant activated factor VII (rFVIIa), haemophilic patients with high inhibitor titres requiring elective orthopaedic surgery can undergo such surgery with a high expectation of success [14–16]. The advent of rFVIIa has made major elective orthopaedic surgery possible in haemophilia patients with high-titre inhibitors, leading to an improved quality of life for these patients. Recombinant FVIIa and FEIBA® appear to be efficient haemostatic product for surgery in patients suffering from haemophilia A and B with inhibitors. Thorough analysis of each case as part of a multidisciplinary team will allow us to perform elective orthopaedic procedures in patients with inhibitors [16].

Conclusions

The orthopaedic problems of haemophilia and the surgical techniques most frequently performed by orthopaedic surgeons for haemophilia patients are summarized in Table 1.1. Sometimes it is recommended to carry out two or three orthopaedic surgical procedures in a single operative session, with the aim of solving the functional problem in a more global way, which usually is polyarticular. There is no doubt that this involves a greater anaesthetic risk, but avoids the repetition of surgical procedures and reduces factor consumption.

Close co-operation between haematologists, orthopaedic surgeons, rehabilitation physicians, paediatricians, psychologists, physiotherapists and nurses is paramount for the satisfactory outcome of all orthopaedic surgical procedures described in this chapter. There is no doubt that continuous prophylactic clotting factor replacement (prophylactic therapy) is the way to avoid the orthopaedic problems of haemophilia that can still be seen today. Until such a goal can be realized, the orthopaedic surgeon must continue to perform arthrocentesis, synoviorthesis, synovectomy, tendon lengthening, débridement, osteotomy, joint replacement, osteosynthesis of fractures and other less frequent surgical procedures for persons with haemophilia. The chapters that follow analyse new perspectives in the treatment of haemophilic joints.

Table 1.1 Main orthopaedic complications of haemophilia and their recommended solutions.

| 1 | Haemarthrosis: aspiration (arthrocentesis) |
| 2 | Chronic synovitis: radiotherapy and surgical synovectomy |
| 3 | Fixed-joint flexion contracture: tendon lengthening, external fixators and extension osteotomy |
| 4 | Arthropathy: ulnar nerve release, cheilectomy, curettage of bone cysts, joint débridement, alignment osteotomy, arthrodesis and total joint arthroplasty |
| 5 | Haematoma and haemophilic cysts: opening of compartment syndromes and removal of cysts (pseudotumours) |
| 6 | Fractures: bone stabilization by closed or open methods |

References

Pathogenesis of haemophilic synovitis and arthropathy

G. Roosendaal and F.P.J.G. Lafeber

Introduction

Haemophilia is an X-chromosome-linked disease characterized by an increased and life-long tendency to haemorrhage as a result of a deficiency or functional defect of coagulation factor VIII or factor IX. The higher the factor VIII or factor IX coagulant activity the fewer the clinical problems. In severe haemophilia, affecting 45% of the patients, serious bleeding can occur spontaneously especially in the larger joints. In severe haemophilia 85% of all bleeding events occur in joints, and 80% of these events affect the ankle, knee or elbow; the hip and shoulder are affected to a lesser extent. There is no satisfying explanation as to why bleeds occur so frequently in joints compared with other sites and why there is a predisposition for the knee, ankle and elbow joints, but it has been suggested that mechanical factors are important in this respect.

The direct symptoms or ‘short-term’ effects of joint bleeding are pain, swelling, warmth and muscle spasm. With appropriate treatment the lesion settles in a few days as the blood is reabsorbed. The ‘long-term’ effects of joint bleeding are more serious. Repeated episodes of intra-articular bleeding cause damage to the joint (haemophilic arthropathy), leading to deformity and crippling [1,2]. The delay between joint bleeding and the subsequent joint damage makes it difficult to establish the exact pathogenetic mechanism of haemophilic arthropathy.

As a result of recurrent haemarthroses, specific changes occur in synovium and cartilage which finally result in total destruction of the joint. This process is called haemophilic arthropathy [3–8]. Haemophilic arthropathy is the most common cause of morbidity in patients with haemophilia and has a great impact on the quality of life of patients. Haemophilic arthropathy generally becomes evident at an early age (15–25 years), and because haemophilia patients nowadays have a normal life expectancy, the number of disease years per patient (concerning joint disease) can be as high as 50. This is in contrast to other musculoskeletal diseases, such as osteoarthritis and rheumatoid arthritis, which usually start at an older age and as a consequence have less impact on the labour force and on social security costs. However, when it comes to the treatment of the most common complication of haemophilia, haemophilic arthropathy, consensus is hard to find. Definitions of, for example, the severity of a bleeding, the degree of joint damage or the type of synovitis are a source of discussion and misunderstanding. The treatment of (chronic) synovitis and joint damage varies enormously worldwide and is frequently based on tradition and local practice. The use of physical therapy, immobilization, intra-articular corticosteroids, synoviorthesis with rifampicin or radiosynoviorthesis, open or arthroscopic synovectomy, laser synovectomy or general orthopaedic procedures is a subject of controversy and discussion. While some of the differences in the mode of treatment are related to the high costs of clotting factors needed for the treatment of haemophilic arthropathy, another important reason for these differences in the mode of treatment is the lack of knowledge about the mechanisms responsible for haemophilic arthropathy.

The pathogenetic mechanisms of haemophilic arthropathy are not precisely known. It is generally accepted that there is a relation between recurrent intra-articular bleeding and the long-term development of joint damage. However, little is known about the effects of blood on joint structures; for instance, the amount of blood or the number of bleeding episodes that initiate joint damage. Such questions are difficult to answer. Although investigators agree that a certain number of bleeding episodes eventually result in clinically evident synovial tissue changes and in cartilage damage, the question remains as to how many bleeding events are needed to start irreversible damage, whether it is clinically evident or not. Fischer et al. [9] described that prophylaxis with clotting factors after the first two haemorrhages in life is more beneficial in the long term than starting with prophylaxis after more than three haemorrhages. More insight into this problem may have consequences for the prophylactic treatment of patients with haemophilia [10,11].

Synovial changes and destruction of articular cartilage are the most prominent events in haemophilic arthropathy. Cartilage contributes to the extraordinary properties of joints and allows for the distribution of high compressive loads and stable movement of the joint with a very low level of friction. There are no reports indicating that the cartilage of patients
with haemophilia (before joint destruction starts) is different from that of healthy people.

Several different joint disorders, degenerative ones (e.g. osteoarthritis), inflammation-mediated ones (e.g. rheumatoid arthritis) and blood-induced ones (e.g. haemophilic arthropathy) result in cartilage damage and changes in synovial tissue. Several mediators are involved in these changes; e.g. enzymes, cytokines and oxygen metabolites. Current concepts, which are based on experimental in vitro studies and clinical experience, hold that the synovium becomes cataphobically active because of the exposure to blood components and as a result induces cartilage destruction. Synovial iron deposition, which is easily detectable by magnetic resonance imaging (MRI), is suggested to be indicative of the severity of haemophilic arthropathy. However, these concepts are based on only a limited number of studies. In comparison to our knowledge about osteoarthritis and rheumatoid arthritis, little is known about the mechanisms of cartilage damage in haemophilic arthropathy. The pathophysiology is possibly multifactorial in origin and includes degenerative cartilage-mediated and inflammatory synovium-mediated components.

**Haemophilic synovitis**

It is recognized that the repeated extravasation of blood into the joint cavity is the factor responsible for synovial and cartilage changes [8,12]. Synovial changes are thought to precede cartilage changes. The progressive accumulation of iron from red blood cells (RBC) removed from the joint cavity by synovial macrophages over time during successive intra-articular haemorrhages was postulated to be the trigger for synovial inflammation. This synovial inflammation would ultimately lead to joint damage that becomes evident years after the first bleeding episode has occurred [13]. An important characteristic of synovial changes is the deposition of iron (haemosiderin) in the synovium, both in the synovial lining and the supporting layer. Haemosiderin deposits in the lining appear as discrete granules, scattered throughout the cytoplasm of the cells. The haemosiderin deposits in the supporting layer appear as dense aggregates, both intracellular and extracellular. Because of an abundance of synovial iron deposits, the synovium appears macroscopically to be brownish (haemosiderotic). Experimental haemarthrosis induces synovial changes resembling those seen in human haemophilic patients. The haemosiderin deposits are thought to induce synoviocyte hypertrophy (resulting in villi), and (in the subsynovial layer) neovascularization (resulting in increased vascularity).

Another suggested effect of the haemosiderin deposits is an infiltration of the synovial membrane with lymphocytes, although follicles of lymphocytes as can be seen in the synovial membrane of rheumatoid arthritis have not been observed. In general, the morphological picture of the synovium differs with the age of patients and probably correlates with the number of intra-articular bleedings; in younger patients being villous proliferative and hyperaemic, and in older patients flat synovium with fibrosis can be seen. Compared to inflammatory arthropathies such as rheumatoid arthritis, there are only mild inflammatory changes. Synovial iron deposits as a result of recurrent intra-articular haemorrhages are also found in other joint disorders such as pigmented villonodular synovitis, haemangiomas of the synovial membrane and haemosiderotic synovitis. These joint disorders all result in joint damage resembling haemophilic arthropathy, which suggests that synovial iron deposits indeed play an important part in the pathogenesis of blood-induced cartilage damage [14,15]. Accumulation of iron as a degradation product of haemoglobin may be a direct stimulus for the proliferation of synoviocytes and an attractant of inflammatory cells; the subsequent production of enzymes and cytokines could lead to the destruction of articular cartilage [16,17].

In a recent study it was found in patients with haemophilia who went for elective orthopaedic surgery of the knee that in all patients the synovial tissue showed areas with a haemosideritic appearance adjacent to areas of normal appearance [18]. This finding provided a model for an analysis of the effect of synovial iron deposits in synovial tissue. The macroscopic appearance corresponded closely to the histological iron deposits and, in addition, to the inflammatory and catabolic activity of the tissues. The results show that the iron deposits at localized sites in the synovium are associated with the production of pro-inflamatory cytokines and an ability to inhibit the formation of human cartilage matrix. This supports the hypothesis that iron has a leading role in the induction of synovial changes and the consequent production of catabolic mediators harmful to articular cartilage. It is not clear whether haemosiderin is directly involved in the stimulation of cytokine production; it seems more likely that phagocytosis by synovial cells and blood macrophages released into the haemarthritic joint leads to the stimulation of cytokine production. The inflammatory changes in haemosiderotic synovial tissue, as determined histologically, are mild compared with those from tissue with inflammatory joint disease such as rheumatoid arthritis, but the production in vitro of catabolic mediators such as interleukin 1 (IL-1), IL-6 and tumour necrosis factor α (TNFα) is comparable to that found for synovial tissue from patients with rheumatoid arthritis [unpublished data]. The potential for damage by haemosiderotic synovial tissue underlines the importance of early diagnosis and treatment of chronic synovitis in haemophilic patients.

MRI makes it possible to demonstrate hypertrophic synovial tissue with haemosiderin depositions in joints with chronic synovitis. Apart from reducing the frequency of bleeding episodes, it can be suggested that synoviorthesis or early synovectomy may slow down the joint deterioration in haemophilic arthropathy. The presence of significant synovial iron deposits may be an indication for synoviorthesis or synovectomy to reduce consequent joint damage.
**Haemophilic arthropathy**

A considerable number of reports concerning blood-induced joint damage suggest that synovial changes have a leading role in the development of joint damage. In experimentally induced haemarthrosis, one of the earliest effects observed is proliferation and inflammation of the synovial tissue (synovitis). Synovial changes are thought to induce and therefore precede the changes in cartilage. However, there are also observations that question whether this is the only and the initiating mechanism of joint damage in haemophilia [19]. These hold that intra-articular blood has a direct harmful effect on cartilage before, and independent of, synovial changes and suggest that joint damage may occur before synovial inflammation is evident; primarily there may be damage of articular cartilage with synovitis as a consequence.

The latter concept is substantiated by findings in a human *in vitro* model of haemarthrosis [20–22]. Biochemical and metabolic analyses showed that subtle but irreversible changes in chondrocyte metabolic activity occurred in human cartilage after a short exposure to blood *in vitro*. Clinically, these changes cannot be detected but they may have a role in the pathogenesis of blood-induced arthropathy. Human articular cartilage consists of a relatively small number of chondrocytes embedded in a relatively large amount of extracellular matrix. This extracellular matrix consists mainly of collagen and proteoglycan. There is a continuous turnover of these matrix components, with a delicate balance between synthesis and breakdown [23]. Several mediators, such as growth factors, enzymes, cytokines, oxygen metabolites and their natural inhibitors, are involved in maintaining this balance but are also involved in cartilage damage when there is an imbalance between synthesis and breakdown. Results of these studies show that a relatively short exposure (4 days; the natural evacuation time of blood from a joint) of human cartilage to whole blood in concentrations up to 50% (blood concentration during haemarthrosis approaches 100%) induces long-lasting damaging effects. There is marked inhibition of matrix formation (proteoglycan synthesis) and increased breakdown, i.e. release of matrix components (proteoglycan release), resulting in a continuing loss of matrix (proteoglycan content). The initial biochemical changes seen in these studies were not accompanied by either histologically detectable or macroscopic changes. However, these studies reveal that cartilage changes induced by short-term exposure to whole blood result in continuing inhibition of proteoglycan synthesis, accompanied by a continuing decrease in proteoglycan content. In the long term, histological and macroscopic changes would likely follow.

To acquire more insight into the mechanism of blood-induced cartilage damage it is crucial to know which blood components are responsible for cartilage changes. Human *in vitro* studies reveal marked inhibition of proteoglycan synthesis by mononuclear cells (MNC). This effect of MNC has been reported before; e.g. in studies of blood from patients with rheumatoid arthritis. The proposed mechanisms include, among others, effects of lysosomal enzymes and catabolic cytokines. However, none of these effects proved to be long-lasting. In recent *in vitro* studies whole blood showed long-lasting inhibition of proteoglycan synthesis and enhancement of glycosaminoglycan (GAG) release in contrast to isolated components. Only the combination of MNC and RBC revealed effects comparable to whole blood. A possible explanation for the irreversible damage by this combination is the conversion of oxygen metabolites produced by the monocytes in the MNC population to the toxic hydroxyl radicals catalysed by iron supplied by RBC [24,25].

**New concepts**

These results, indicating a direct harmful effect of blood on cartilage, do not exclude the important role of reported synovium-induced cartilage damage. In addition to ‘synovium-related’ changes (certainly important in the long run), cartilage damage may be induced initially by blood. This cartilage damage may in turn induce inflammatory responses. Recent canine *in vivo* studies corroborate these concepts [26,27]. These studies were undertaken to test the hypothesis, based on results of *in vitro* studies, that a short exposure to blood during a single or a limited number of bleeding events results in changes that inevitably lead to joint destruction.

**Experimental cartilage changes**

Results of canine *in vivo* studies show that canine cartilage exposed *in vivo* to whole blood for a relatively short time (4 days) exhibits long-lasting biochemical and histochemical changes of the cartilage matrix and changes in chondrocyte metabolic activity as well as changes in the synovium. These changes are predictive of irreversible joint damage in the long term. The changes with respect to loss and content of proteoglycans persisted for at least 16 days. The total proteoglycan content remained low despite the enhanced synthesis of proteoglycans on day 16. The shift from an inhibition to a stimulation of proteoglycan synthesis from day 4 to day 16, while the decreased proteoglycan content remained low, suggests that the increase in proteoglycan synthesis was an ineffective attempt to repair cartilage. A similar ineffective enhancement of proteoglycan synthesis has also been described for osteoarthritic cartilage.

Swelling of cartilage is an early sign and an important marker of osteoarthritic cartilage and is believed to be caused by disruption of the collagen network. The cross-linked three-dimensional fibrillar network of collagen is responsible for the tensile strength of cartilage, and disruption of this network by proteolytic enzymes, excessive mechanical loading and oxygen metabolites leads to pathological conditions. In this canine *in vivo* study a slightly, but statistically significant, higher percentage of degraded collagen was detected in the injected joint compared to the control joint on day 4, indicating that even
a short exposure to intra-articular blood can damage the collagen network, with a possible detrimental effect in time. Oxygen metabolites formed during intra-articular bleeding might be involved in this process. This would suggest that the short exposure to blood itself, and not the synovitis that was evident on day 16, is involved in this collagen-destructive process.

These canine in vivo findings concerning the effects of blood on cartilage proteoglycan and collagen are consistent with the findings of Convery et al. [28]. During the continuous presence of blood in 14 mongrel dogs they found morphological changes of the articular cartilage after 16 weeks, but there was a significant decrease in GAG content after only 4 weeks. The total collagen content was significantly altered after 12 weeks. Biophysical analysis of the cartilage surface after 8 weeks showed that the tissue was more deformable and less resistant to shear than the control cartilage. In addition, Parsons et al. [29] found in an animal model that the continuous presence of blood in the joint for 10 days resulted in cartilage that was significantly more compliant than normal. They attributed these changes to the loss of proteoglycan. We suggest that intra-articular blood-induced collagen damage may also have been involved and that such changes take place after a short exposure to intra-articular blood.

**Experimental synovial changes**

In this canine in vivo study the changes in synovial tissue shortly after exposure to blood were restricted to mild synovial inflammation. The synovial tissue did not have cartilage-damaging potential. Because at this early time point cartilage changes were already evident, this observation does not support the general concept that changes in synovial tissue are a prerequisite for, and precede, the changes in cartilage. On the contrary, it corroborates in vitro findings that cartilage changes occur after a short exposure to blood, before the involvement of synovial inflammation. Two weeks after exposure to blood, the inflammation of synovial tissue was accompanied by cartilage-destructive properties. Apparently it takes time for the synovium to acquire cartilage-damaging activity, which might depend on the phagocytosis of blood cells or on the accumulation of haemosiderin and subsequent production of cytokines and matrix metalloproteinases. Thus, blood first has a direct effect on cartilage, presumably as a result of the iron-catalysed formation of destructive oxygen metabolites. Whether these changes are essential for the subsequent synovial changes remains to be elucidated. Blood itself may cause these synovial changes.

These recent studies show that synovitis is involved, but that it is not the only mechanism in joint damage caused by intra-articular bleeding. This pathogenetic concept does not contradict the current concept of blood-induced cartilage damage in which synovial changes are thought to have an important role. Several pathological processes are possibly involved, some of them occurring in parallel and others sequentially.

**Conclusions**

The pathogenetic mechanism of haemophilic arthropathy is multifactorial and includes degenerative cartilage-mediated and inflammatory synovium-mediated components. Intra-articular blood first has a direct effect on cartilage, presumably as a result of the iron-catalysed formation of destructive oxygen metabolites, and then it affects the synovium. Thus, both processes occur in parallel, and while they influence each other they probably do not depend on each other. This concept resembles degenerative joint damage as found in osteoarthritis. These processes finally result in a fibrotic and destroyed joint. It is unknown if and, if so, when a point of no return is reached. More insight into the mechanisms of haemophilic arthropathy may have consequences for the (prophylactic) treatment of patients with haemophilia. Unravelling the mechanism of haemophilic arthropathy as well as defining a possible point of no return is still the subject of research.

Haemophilia is an X-chromosome-linked disease characterized by an increased tendency to haemorrhage. As a result of recurrent haemarthroses, specific changes occur in synovium and cartilage. This process is called haemophilic arthropathy. The pathogenetic mechanisms involved are not precisely known. Current concepts, which are based on experimental in vitro studies and clinical experience, hold that the synovium becomes catabolically active because of the exposure to blood components and as a result induces cartilage destruction. A considerable number of reports concerning blood-induced joint damage suggest that synovial changes have a leading role in the development of the joint damage and therefore precede the changes in cartilage. However, there are also observations that questions whether this is the only and the initiating mechanism of joint damage in haemophilia. These hold that intra-articular blood has a direct harmful effect on cartilage before synovial changes and suggest that joint damage may occur before synovial inflammation is evident. Primarily, there may be damage of articular cartilage with synovitis as a consequence.

These studies show that synovitis is involved, but that it is not the only mechanism in the joint damage caused by intra-articular bleeding. These findings do not contradict the current concept of blood-induced cartilage damage in which synovial changes are thought to play an important part. Several pathological processes are possibly involved, some of them occurring in parallel and others sequentially. Possibly, intra-articular blood first has a direct effect on cartilage, and then it affects the synovium. Thus, both processes occur in parallel, and while they influence each other they probably do not depend on each other. This concept resembles degenerative joint damage as found in osteoarthritis.

**References**

THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES


CHAPTER 3

Haemophilic haemarthrosis

M. Betsy and M.S. Gilbert

Introduction

Volkmann, in 1868 [1], pointed out that, in patients with haemophilia, haemarthrosis could occur either spontaneously or as a result of insignificant trauma. In 1892 Konig [2] gave a detailed description of the clinical findings that occurred following repeated haemarthrosis and showed that destructive arthritis was a result of repeated intra-articular bleeding. A lack of understanding of the coagulation defect and the unavailability of haematological treatment led him to suggest mild compression and immobilization as treatment for these haemarthroses. In the 1950s, Jordan [3] used cast correction and bracing to control bleeding and correct deformity. He termed intra-articular bleeding and the subsequent arthritis 'haemophilic arthropathy.' By the 1960s, the availability of concentrates of factor VIII and factor IX ushered in the modern era of haemophilia treatment.

Forrai [4], in 1979, pointed out that:

Haemophilic arthropathy is a single long process which starts as an acute intra-articular haemarthrosis and eventually leads to disabling regression through several episodes of bleeding, destruction of cartilage, and degenerative changes of the subchondral bony tissues. Its course is slow and progressive, although not without episodes of relative comfort, and there are no specific clinical, pathomorphologic or radiologic stages of the disease.

Nevertheless, for practical reasons, some sort of staging becomes necessary to characterize the patient's condition. Konig [2] divided the destructive process into three stages.

1. The stage of the first bleeding, the haemarthrosis of the bleeders.
2. The inflammatory stage, panarthritis in the bleeder's joint.
3. The regressive stage, which causes permanent deformity of the bleeder's joint, the contracture of the joint.

DePalma [5] in 1967 further divided the arthropathy into four grades and, more recently, Arnold and Hilgartner [6] have described five stages in which they attempt to classify the progressive radiological features and correlate them with the clinical state. However, in the authors' opinion there is little correlation between the clinical and radiological states. Jordan [3] also stated that, 'It is amazing to see how a marked degree of articular destruction with extensive thinning of the cartilage leaving a joint space only a few millimetres is compatible with considerable range of motion.' Because of this, the Musculoskeletal Committee of the World Federation of Haemophilia developed a clinical classification to be used alongside the radiological classification developed by Pettersson and Gilbert [7]. These complementary classifications closely reflect the clinical and radiological situation but have proven rather cumbersome for routine use. At the present time, there is no commonly accepted classification. Recently, Manco-Johnson and Funk, and Rodriguez-Merchan and de la Courte, have evaluated this situation and they discuss this in detail in Chapters 7 and 8.

Clinical course

If untreated, almost every severe haemophilic will experience a haemarthrosis during the first decade of life, and it is rare to enter the third decade without the development of arthropathy. There is no difference in the clinical manifestation of factor VIII and factor IX deficiencies. van Creveld et al. [8] in 1971 pointed out that despite early treatment, joint degeneration is progressive. Levine [9] demonstrated that even on home care with early treatment, destruction of the joint will continue, and new joint involvement can be noted. Early treatment was therefore shown to modify but not eliminate the musculoskeletal manifestation of this disease.

Any diarthrodial joint in the extremity may be affected. Jordan [3] and Duthie et al. [10] suggested that the knees, elbows and ankles are most commonly involved, in decreasing order of frequency. Hip, shoulder and wrist involvement is less common, and bleeding into the small joint of the hands and feet without significant trauma is not common. No one has adequately explained why certain joints are more commonly involved than others. Jordan [3] proposed, and it has been generally accepted, that some form of trauma precedes any haemarthrosis. 'Spontaneous haemarthrosis' is probably secondary to micro or unappreciated trauma. It can be assumed that trauma to the synovium, which is the site of initial bleed-
THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES

ing, is more common in the complex joints. Because of the large synovial surfaces present within knee and elbow and because of the rotary stresses within these joints, bleeding is initiated. The frequency of bleeding at the ankle can be attributed to the fact that this is the most commonly traumatized joint. However, it must be appreciated that these are hypotheses that have never been proven.

Most recently, the clinical pattern of joint bleeding seems to have changed. In a review of patients treatment at Mount Sinai Hospital, New York, USA, we have shown that in patients under 20 years, the most commonly involved joint is now the ankle [11]. We have attributed this to the fact that our patients are participating in sports and living normal active lives. However, this does not account for the decreasing frequency of bleeding in the knee that was noted in our series.

The clinical picture of a haemarthrosis is characterized by pain, swelling and limitation of motion. A prodromal ‘aura’ has been described by many patients. They describe it as a painless but distinct sensation, which the patient appreciates prior to the onset of the pain and swelling. The aura is usually followed by mild stiffness and lasts up to 1 h. If left untreated, the joint will then become swollen and warm, and the clinical manifestations of acute haemarthrosis become evident. Flexion, limitation of motion and secondary muscle spasm will follow.

It has been postulated that bleeding will continue until the intra-articular pressure is raised to a point where the bleeding vessels are occluded. The clinical course following a haemarthrosis is variable. It may seem to resolve completely but, at other times, recurrent bleeding will recur despite ‘adequate treatment’. Joints displaying a tendency towards such recurrent bleeding have been termed ‘target joints’ by Aronstam et al. [12]. We believe that this corresponds to the second stage described by Konig. Complete resolution is theoretically possible, but we believe that there are some persistent changes that cannot completely resolve.

Clinically, it is noted that the pain responds quickly to replacement of the missing clotting factor. If treatment is instituted almost immediately, the other objective findings may not develop. Progression may take one of three clinical courses.

1 Resolution as noted before may be seen. Some microscopic damage within the synovium and articular cartilage probably occurs.

2 There may be no resolution and an inflammatory state persists. We believe that this is a result of persistence of bleeding within the joint. This state has been called ‘haemophilic synovitis’. One may see thickening of the synovium and an effusion that does not respond to replacement of the missing clotting factor.

3 Development of arthritis over a variable period of time. This is the end-stage of arthropathy, which has been described by Konig and Jordan. It is characterized by limitation of motion, crepitus and deformity.

Chronic bleeding and inflammation can cause the early appearance of epiphyseal growth centres, epiphyseal overgrowth and longitudinal overgrowth. The clinical manifestations of longitudinal overgrowth are most obvious at the knee, where the growth plates contribute almost 70% to the length of the extremity. Kingma [13] has shown that affected limbs are most commonly longer following bleeding on one side. This may not be evidenced at first as there is an associated flexion contracture, but when this is corrected the leg length discrepancy becomes obvious. Circumferential enlargement of the epiphyseal centre is manifested and accentuated by the associated muscle atrophy. Also described is premature effusion of the epiphysis to the metaphysis, which can cause shortening and angular deformity. Caffey and Schlesinger [14] described this as early as 1940.

Diagnosis

The diagnosis of an acute haemarthrosis, despite the availability of advanced imaging techniques, is almost entirely a clinical diagnosis based on the patient’s symptoms and, to a lesser extent, on the physical findings. The imaging techniques have been described in detail by Nuss and Kilcoyne in Chapter 5. Once the swelling, warmth, limitation of motion and flexion contracture are manifested, the diagnosis becomes easy, but treatment becomes less effective. Therefore, one must treat even if the diagnosis is suspect. Frequently, it is difficult to determine whether minimal pain or stiffness is secondary to an acute haemarthrosis or to arthropathy but, as Levine [9] says, ‘When in doubt treat’.

Treatment of haemarthrosis

The optimal treatment of acute haemarthrosis involves input from the haematologist, orthopaedic surgeon and rehabilitation specialist. However, it must never be forgotten that the mainstay of treatment is the normalization of the coagulation mechanism by replacement of the missing clotting factor. Ideally, one should raise the level of the missing factor so as to prevent any bleeding episode. The efficacy of this protocol, termed ‘prophylaxis’, has been well demonstrated in several studies [15–17].

That this is the ideal form of treatment cannot be gainsaid. It is the ideal to which we all aspire until this disorder is either genetically controlled or cured, but the reality remains that most patients in the world have little or no factor available for treatment and that, in most countries, economic and social strictures limit therapeutic protocols to treatment of bleeding episodes rather than prevention. This form of treatment, termed ‘episodic care’, is the most common protocol used in developed countries. Ideally, the patient or a family member has been taught by the haemophilia team to infuse the factor as early as 1940.

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30–50 IU/dL. To achieve such a level in a patient with severe haemophilia, 15–25 IU/kg factor VIII and 30–50 IU/kg factor IX may be required. A single infusion should be sufficient to stop the bleeding if treatment is started quickly following symptoms. If the response is not rapid, medical evaluation should be sought within 24 h. It is our recommendation that any bleeding episode at the hip be treated immediately at home and that the patient should come to the haemophilia centre for evaluation by the haematologist and orthopaedic surgeon.

Adjunctive modalities include analgesia, rest or immobilization and anti-inflammatory medication. Analgesic requirements are beyond the scope of this chapter other than to state that all aspirin and aspirin-containing compounds must be avoided and that narcotics must be used judiciously. It has been our experience that paracetamol with or without codeine is usually adequate for control of pain and has minimal addictive properties. A sling is usually sufficient for immobilization at the shoulder or elbow; a removable splint can be used at the knee. Once pain and spasm are controlled, the immobilization should be discontinued. It has been suggested that the inflammatory response to blood within the joint cavity can be lessened by the early administration of oral steroids and several papers have recommended their use. They are not used at most centres at the present time, and we do not routinely use oral steroids for an acute haemarthrosis but they may be used judiciously for control of pain if arthropathy has developed.

The role of joint aspiration remains controversial. Early treatment, ideally used before swelling occurs, limits the need for this procedure. Our indications for aspiration are as follows.

1 A tense haemarthrosis that requires narcotics for control of pain.
2 A haemarthrosis that does not respond within 24 h to adequate replacement therapy.
3 Suspicion of septic arthritis as manifested by an elevated temperature or an unusual pain pattern.
4 Bleeding into the hip. This may be devastating because avascular necrosis has been seen following only one bleeding episode. Lessening the pressure in the joint capsule may help limit the compression on the vessels and decrease the chance or extent of avascular necrosis. This joint should be aspirated under radiological control.

If joint aspiration is indicated at the knee, elbow or ankle, it should be performed with a large-bore needle (no. 16 is recommended). Factor levels of 100 IU/dL should be achieved at the time of aspiration. Immobilization and compression following the aspiration should be considered.

Following any haemarthrosis, a supervised rehabilitation programme must be started immediately. Isometric exercises can be started straight away. As soon as the pain is controlled, range of motion exercises should be started followed by a generalized strengthening programme. The role of physical therapy and rehabilitation is discussed in detail in Part 5 of this book.

References

CHAPTER 4

Haematological substitutive treatment of haemophilic haemarthroses

M. Quintana, J. Gracia, V. Jimenez-Yuste, J. Gago, A. Villar and F. Hernandez-Navarro

Introduction

Musculoskeletal bleeding is the most common manifestation of severe haemophilia. Most of the patients affected by moderate or severe haemophilia have had at least one muscle or joint bleeding episode. The resulting arthropathy and muscle contractures are the main cause of morbidity and need treatment with factor concentrates. The disposal of these factor concentrates has produced an important change in the natural history and treatment of haemorrhagic arthritis. Self- or home-treatment, which facilitates prompt treatment, helps avoid the development of degenerative arthritis [1]. With prophylactic treatment, arthropathy can be avoided.

Joint bleeding or haemarthrosis episodes are one of the most important complications in haemophilic patients because of a variety of causes, which include their frequency, the early age at which they start appearing (when a child starts walking) and the medical and psychosocial problems that frequent, painful, limiting and disabling haemorrhages bring to the patient. In addition, repeated joint bleeding episodes lead to complete destruction of joint components; this damaged joint indirectly affects other joints and the whole musculoskeletal system is affected.

The relation between joint disease and haemophilia has a long history, since it was recognized by Otto in 1803. Dubois, in 1838, recognized joint bleeding as a cause of arthritis in haemophiliacs. In the International Orthopaedic Outcomes Study, it was established that the mean annual number of haemorrhagic episodes in patients with severe haemophilia was 23.3 ± 17.2; haemarthroses represented 15.0 ± 12.5, which is 65%. In our experience, haemarthrosis represents 70% of all bleedings in these patients, in some cases manifesting in more than 40 episodes annually.

Why do haemophiliacs’ joints bleed while those of patients with other coagulation disorders seldom do?

There is no known explanation for such a high number of haemarthroses in haemophilic patients and no known reason for them to be located more often in the knees, elbows and ankles. Anatomical, biochemical and mechanical factors could contribute to an initial bleeding and to the persistence of haemorrhagic arthritis. The mechanical factor seems to be the most important because haemarthroses appear when the child starts walking, they are more frequent in the legs than other joints, and severe arthritis develops in the dominant side of the body and is more frequent in ‘hinge-joints’ [2].

The bleeding probably comes from the capillaries of the subsynovial plexus of the joint, which are in the juxtacavitary surface [3]. These capillaries are different to those of deeper subsynovial capillaries which are used for a fast exchange of electrolytes and water [4]. There is no ultrastructural difference in the synovium of joints that bleed more often than others. Nevertheless, the particular distribution of synovium in knees, elbows and ankles could make these joints more vulnerable to injury.

The lack of thromboplastic activity in the synovium, besides the deficiency in the coagulation intrinsic pathway, contributes to a joint haemorrhage [5]. Even though normal synovium has traces of fibrinolytic activity, it has been demonstrated that it is increased in haemophilic patients [6]. This could self-perpetuate the bleeding episodes in a damaged joint. This fact may explain why some patients with similar factor level to others have less bleeding episodes [6]. There are no differences in joint looseness, but it can be demonstrated that age is directly related to the frequency of haemarthrosis.

Clinical features of haemophilic arthropathy

Three well-differentiated phases can be distinguished in the progression of haemophilic arthropathy:

1. acute haemarthrosis;
2. chronic synovitis; and
3. degenerative arthritis.

Acute haemarthrosis

Severity of factor deficiency is directly related to the frequency of joint bleeding. Although bleeding can occur in any target
joint, the knee, elbow and ankle of the dominant side is the most common location. Diagnosis of a haemarthrosis in a haemophilic patient is not difficult. It is frequently preceded by the patient’s perception of an aura or tingling sensation in the joint, before presenting typically as acute pain. Premonitory symptoms may vary among patients. The bleeding into the joint will cause the patient to place the joint in a position of maximum volume, which is generally in slight flexion; in addition, signs and symptoms of inflammation appear.

Such haemarthrosis may occur spontaneously or as a result of trauma. In the absence of previous trauma, some complementary tests are needed to confirm the diagnosis. A simple X-ray is sometimes enough to rule out a fracture. Magnetic resonance imaging (MRI) is necessary to detect injuries in soft tissues, such as ligaments or menisci. In HIV-positive patients a septic arthritis should be suspected which should be ruled out with an arthrocentesis and examination of synovial fluid.

**Chronic synovitis**

Recurrent haemarthroses will inevitably lead to significant hypertrophic synovitis in patients with haemophilia. The beginning of this phase may be difficult to establish. If the synovitis is not controlled, there will be progressive cartilage degradation, ultimately resulting in haemophilic arthropathy with significant functional impairment. The most affected joints are knees, elbows and ankles. The affected joint is often the target joint of haemorrhages.

The main clinical feature is a little painful or intermittently painful inflammation of the joint. Periarticular muscle pain may be present with some limitation of mobility. Clinical features and symptomatology will establish the diagnosis. Radiology may be useful in determining the extent of the damage to cartilage and bone. This synovitis phase may last for several months or even years and the volume of joint effusion may vary depending on the severity of bleeding. Fibrous tissue appears in hypertrophic synovium.

**Degenerative arthritis**

Degenerative arthritis may be defined as the maintenance of chronic synovitis for more than 6 months. Clinical features are those of the final phase of synovitis. Deformities in haemophilic patients are more severe because the destruction process starts before the epiphyses have been consolidated and because of muscular contractures caused by muscle haematomas. The earliest radiological sign of degenerative arthritis is the reduction or even loss of intra-articular space (loss of cartilage), which is secondary to osteoarticular changes. This change can manifest as subchondral sclerosis, cyst formation and the presence of osteophytes in the articular surface.

In developed countries, haemophiliacs with chronic or degenerative arthritis can be divided into two groups. One group includes young patients who began receiving replacement therapy with cryoprecipitates or factor concentrates when their arthritis was already established. The second group includes all those patients aged between 20 and 30 years who were treated on-demand in their bleeding episodes and do not have evidence of chronic arthritis in one or two joints.

**Treatment of haemophilic arthropathy**

The main goals of treatment of haemophilic arthritis are to alleviate symptoms, prevent articular damage progression and preserve a functional range of motion. These goals can be achieved by early treatment of haemarthrosis and control of the effects of synovitis. In a patient with an already established degenerative arthritis, joint function can be improved by surgical and physical methods under adequate haemostatic protection.

**Treatment of acute haemarthrosis**

Treatment of acute haemarthrosis requires factor concentrates administration and analgesia. Home- or self-treatment allows prompt treatment of bleeding episodes. In haemophilia A, replacement therapy should reach and maintain serum factor VIII level at 50–100%. In haemophilia B, this level should be no less than 40–60% of factor IX. These levels can be achieved by administering doses of 50 IU/kg of factor VIII and 20–30 IU/kg of factor IX, respectively. However, hip and shoulder haemorrhages require the maintenance of higher serum levels of factor IX for longer periods of time. Replacement therapy should be maintained until joint bleeding has completely stopped. Pain is the main parameter to determine the need for maintenance of replacement therapy. An arthrocentesis is needed in the case of a tensional haemarthrosis or when the physician suspects a septic arthritis; this procedure, nevertheless, should only be performed by experienced personnel, using an aseptic technique and after haemostatic replacement therapy [7].

When joint inflammation does not disappear, despite replacement therapy, the administration of systemic corticosteroids is recommended, although their benefits are unclear [8]. Mobilization must be initiated when bleeding stops and acute pain no longer exists. Temporary immobilization with a splint is only indicated in cases of a severe flexion deformity. When flexion contracture persists, conservative correction is needed (splints). However, surgery may provide adequate correction when conservative procedures fail.

In haemophilic patients with high-responder inhibitors, replacement therapy is more complicated because alternative treatments must be used. All haemophilic patients (A and B) who develop an inhibitor are treated with activated prothrombin complexes or with recombinant activated factor VII. There are two activated prothrombin complex concentrates (aPCCs) on the market: FEIBA® (Baxter Hyland, Glendale, CA, USA) (factor VIII inhibitor bypassing activity) and Autoplex® (Immuno, Austria) (anti-inhibitor coagulant complex). The Haemophilia Centre at La Paz University Hospital, Madrid, has extensive experience of replacement therapy in bleeding
Table 4.1 Therapeutic protocol with activated prothrombin complex concentrates (aPCCs) regarding the severity of bleeding at the Haemophilia Centre at La Paz University Hospital, Madrid.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light bleeds</td>
<td>50–100 IU/kg in a single dose</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>100 IU/kg initial dose, then 50 IU/kg every 12 h</td>
</tr>
<tr>
<td>Very severe bleeds</td>
<td>100–200 IU/kg every 6–8 h</td>
</tr>
</tbody>
</table>

After 24 h check continuity depending on results.

Table 4.2 Results obtained with aPCCs on treatment of haemarthrosis and haematomas in the Haemophilia Centre at La Paz University Hospital, Madrid.

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>100 IU/kg</td>
</tr>
<tr>
<td>Moderate</td>
<td>100 IU/kg, then 50 IU/kg every 12 h</td>
</tr>
<tr>
<td>Severe</td>
<td>100–200 IU/kg every 6–8 h</td>
</tr>
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</table>

After 24 h check continuity depending on results.

Table 4.3 Therapeutic protocol for the treatment of patients with inhibitors at the Haemophilia Centre at La Paz University Hospital, Madrid.

<table>
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</tr>
<tr>
<td>Moderate</td>
<td>100 IU/kg initial dose, then 50 IU/kg every 12 h</td>
</tr>
<tr>
<td>Severe</td>
<td>Then 50 IU/kg check every 12 h</td>
</tr>
</tbody>
</table>

Introduction of prophylactic regimens in haemophilic patients who have not developed inhibitors in the past has allowed that haemarthrosis incidence in children is low and so is the evolution to degenerative arthritis. In these patients prophylaxis is started within their first 6 months of life (primary prophylaxis) or when the first haemarthrosis occurs (secondary prophylaxis). This should be maintained until the age of 18, when the musculoskeletal apparatus is completely developed.

Most recently, FVIIa has been used to treat bleeding in patients with inhibitors in surgery. Lately, activated recombinant factor VII (rFVIIa) has been very successfully used in home treatment of patients with inhibitors. The Haemophilia Centre at La Paz University Hospital, Madrid, uses the following therapeutic protocol: initial dose 120 μg/kg; repeat the dose after 2 and 4 h; reinforcement dose after 6 h to avoid re-bleeding. Other doses are administered depending on clinical evaluation. Lately, mega-doses of rFVIIa (300 μg/kg) have been used as initial dosage; similar doses are administered if pain and inflammation remain. Recombinant FVIIa is given simultaneously with tranexamic acid in a dosage of 500–1000 mg intravenously every 8 h. Another route of administration rFVIIa is by continuous infusion.

Table 4.3 shows the therapeutic protocol at the Haemophilia Centre at La Paz University Hospital regarding the type of inhibitor response, the bleeding severity and the patient’s inhibitor titre. The main aim is to maintain the inhibitor titre at the lowest possible level, while avoiding the use of factor concentrate, reserving it for life-threatening bleeding episodes.

Table 4.3 Therapeutic protocol for the treatment of patients with inhibitors at the Haemophilia Centre at La Paz University Hospital, Madrid.

<table>
<thead>
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<th>Protocol</th>
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<tbody>
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<tr>
<td>Moderate to severe</td>
<td>100 IU/kg initial dose, then 50 IU/kg every 12 h</td>
</tr>
<tr>
<td>Very severe</td>
<td>Then 50 IU/kg check every 12 h</td>
</tr>
</tbody>
</table>

After 24 h check continuity depending on results.

The objective of replacement therapy is to break the vicious circle of ‘haemarthrosis–synovitis–musculoskeletal disfunction–recurrent haemarthrosis’. Treatment must be started before the synovitis has become well-developed. Levels of factor around 0.10 IU/mL for 1–2 weeks should be maintained. After that, prophylactic treatment with 25–50 IU/kg three times per week for factor VIII and twice weekly for factor IX is recommended. At the same time, a rehabilitation programme should minimize muscle atrophy and assess joint stability.

Doses of prednisone 1 mg/kg for 1 week followed by 0.5 mg/kg for another week has occasionally been effective [9]. Non-steroidal anti-inflammatory drugs may be useful; COX-2 selective inhibitors having less side-effects at the present time. When, despite these measures, signs of synovitis remain or when repeated haemarthroses occur in a target joint, another therapeutic option such as synoviorthesis or synovectomy [9,10] must be considered.
Treatment of degenerative arthritis

The goal of treatment of degenerative arthritis is the resolution of symptoms and improvement of functional capacity. Different specialists are needed to achieve that aim: nurses, physical therapists, social workers, haematologists, rheumatologists, rehabilitation physicians and orthopaedic surgeons. Haemophilic patients affected by degenerative arthritis can be divided into two groups: one group comprises patients with some (more than one) joints affected and the other group has only one affected joint. The former group have a mean age of 40–60 years and have frequent muscle or joint bleeding episodes. They suffer chronic pain, stiffness and decreasing functional capacity. In these patients analgesia can be difficult to achieve because of the complications that this medication has. Non-steroidal anti-inflammatory drugs may be more useful (ibuprofen has the advantage of being well-tolerated) [11].

The latter group includes patients who have degenerative arthritis in a single joint. In these patients, arthroplasty constitutes the most useful therapeutic option. The study of this procedure is beyond the scope of this chapter. A question that should be answered is what is the effect of factor concentrates in the evolution of haemophilic arthritis? Unfortunately, the answer is not easy because some researchers claim that haemophilic arthritis is a progressive alteration despite adequate replacement therapy. However, most researchers accept that early replacement therapy has better results on the evolution of haemophilic arthritis.

References

Diagnosis by imaging of haemophilic joints

R. Nuss and R.F. Kilcoyne

Introduction

A serious consequence of haemophilia is haemorrhage into the joints [1]. The knee, ankle, and elbow are particularly prone to haemorrhage although haemorrhage also occurs into the hips, shoulders and smaller joints such as the toes and fingers. Recurrent joint haemorrhages, or haemarthroses, lead to haemophilic arthropathy. Haemophilic arthropathy is manifest radiologically as haemarthrosis, effusion, synovial hyperplasia, osteoporosis, subchondral cysts, erosions, cartilage loss, osteophyte formation, ankylosis and pseudotumour formation [2].

Plain radiography

The traditional means of evaluating a joint for haemophilic arthropathy is with plain X-ray. Plain X-ray evaluation is simple as the equipment is generally accessible, the joint views are standard, little time is required to obtain good images, sedation is not required (even for young children), and the changes seen with haemophilic arthropathy are familiar because they are similar to those of other arthritic joints.

In order to assess and follow the course of joint disease in people with haemophilia, two staging systems were developed in the 1970s based on plain X-ray findings. In the USA, the primary staging system is the Arnold and Hilgartner scale. It is a progressive scale reflecting the sequence of changes that occur and can be seen on plain X-ray [3]. The score reflects the worst findings in the joint. The disadvantage of the Arnold and Hilgartner scale is that both early and late findings may be present but the score reflects only the late findings. It has been criticized because the majority of joints garner a score of IV [4]. The Arnold-Hilgartner scale is shown in Table 5.1.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal joint</td>
</tr>
<tr>
<td>I</td>
<td>No skeletal abnormalities; soft tissue swelling present</td>
</tr>
<tr>
<td>II</td>
<td>Osteoporosis and overgrowth of epiphysis; no erosions; no narrowing of cartilage space</td>
</tr>
<tr>
<td>III</td>
<td>Early subchondral bone cysts; squaring of the patella; intercondylar notch of distal femur or humerus widened; cartilage space remains preserved</td>
</tr>
<tr>
<td>IV</td>
<td>Findings of stage III more advanced: cartilage space narrowed</td>
</tr>
<tr>
<td>V</td>
<td>Fibrous joint contracture; loss of joint cartilage space; marked enlargement of the epiphyses and substantial disorganization of the joint</td>
</tr>
</tbody>
</table>

The scale developed in Europe and adopted by the World Federation of Haemophilia is the Pettersson scale [5]. The Pettersson scale gives points per joint abnormality present and the final score is a summation of the individual points (Table 5.2). In contrast to the Arnold and Hilgartner scale, a higher score is achieved if both early and late bone and cartilage abnormalities are present. The two scales also differ in that the Arnold and Hilgartner scale includes soft-tissue changes whereas the Pettersson score does not grade soft-tissue changes.

Plain X-ray evaluation for haemophilic arthropathy has lost favour because it has been shown that the plain X-ray findings underestimate the joint pathology found at surgical evaluation. With plain X-ray evaluation, soft-tissue changes are not well delineated and bone and cartilage damage in the early stages cannot be appreciated. Synovial hyperplasia plays a critical part in the evolution of joint degeneration but with plain X-ray synovial hyperplasia cannot be distinguished from an effusion. With plain X-ray, cartilage loss is determined to be present by inference, because the joint space is narrowed, rather than by direct visualization of cartilage. Early bone cysts or erosions and minimal cartilage loss is missed with plain X-ray.

Ultrasoundography

An alternative radiological method of evaluating haemophilic arthropathy is with ultrasonography. Like plain radiography, it is non-invasive, readily available and relatively inexpensive. There are no detrimental effects associated with its use. The disadvantages of ultrasonography are its inability to penetrate bone and a decreasing resolution with depth so that it is difficult to see deeper regions. The quality of the images is dependent on
Table 5.2 World Federation of Haemophilia Pettersson scale of haemophilic arthropathy [4].

<table>
<thead>
<tr>
<th>Type of change</th>
<th>Finding</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Enlarged epiphysis</td>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Irregular subchondral surface</td>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Subchondral cyst formation</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Narrowing of joint space</td>
<td>Joint space &gt; 1 mm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Joint space &lt; 1 mm</td>
<td>2</td>
</tr>
<tr>
<td>Erosions of joint margins</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Gross incongruence of articulating bone ends</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slight</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pronounced</td>
<td>2</td>
</tr>
<tr>
<td>Joint deformity (angulation and/or displacement between articulating bones)</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slight</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pronounced</td>
<td>2</td>
</tr>
</tbody>
</table>

possible joint score

Score 0–13

the technical equipment, the patient’s tissue constitution and the experience of the physician [6]. Relevant to haemophilia, contrast-enhanced colour Doppler ultrasound has the advantage over grey scale in enhancing flowing blood echoes [7].

Ultrasonography has successfully been used for evaluation of inflammation in the joints of patients with juvenile rheumatoid arthritis. Similar to haemophilia, juvenile rheumatoid arthritis is characterized by inflammation of the synovium. In juvenile rheumatoid arthritis, there is also inflammation of the periarticular tissues including the cartilage, ligaments and capsule of the joint. Using ultrasonic evaluation, Shahin et al. [8] were able to detect a highly significant difference in synovial and cartilage thickness in the knees of children with juvenile inflammatory arthritis as compared with control knees. Doria et al. [9] showed that on B-mode grey scale and colour Doppler ultrasonography, there was a difference in maximum thickness and longitudinal diameter of the synovial membrane in juvenile idiopathic arthritic knees that were symptomatic or quiescent at the time of imaging as compared with control knees. When intravenous contrast (SHU 508) was administered and colour Doppler ultrasound obtained, even in children with subclinical disease, articular inflammation could be appreciated.

Recently, Klukowska et al. [10] reported on the use of ultrasonographic evaluation of haemophilic knees in children. They found ultrasound useful for evaluation of fluid, synovium and cartilage. There was a correlation between the degree of cartilage damage detected with ultrasonography and the Pettersson scores based on plain X-ray.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has advantages over plain X-ray and ultrasound evaluation of a joint by being multiplanar, providing excellent soft-tissue contrast and supporting qualitative volumetric assessment of synovial hyperplasia. MRI depicts cartilage and bone abnormalities earlier and more clearly than ultrasound. Although MRI of a joint is more expensive, less accessible, may require sedation in a child and is more difficult to interpret than plain X-ray evaluation, it is an excellent means of evaluating haemophilic arthropathy [11–16].

MRI T1-weighted images (fat-sensitive) are important for showing anatomical detail but most pathological findings have an increase in tissue T2 values so T2-weighted images (water-sensitive) are preferable for musculoskeletal imaging. In haemophilic joints, where blood or effusions are often present, the increase in T2 is because of the very bright signal which is made by the presence of fluid. An alternative to conventional T2-weighted spin-echo images, which require longer repetition times, is the use of gradient echo pulse sequences, indicated as T2*.

Gradient echo supports shorter repetition times so imaging time is reduced and adequate water sensitivity is obtained. It is possible to obtain three-dimensional gradient echo images with thin contiguous sections which have high-spatial resolution so small structures and lesions can be appreciated [17]. Figure 5.1 shows a large knee effusion.

Synovial hyperplasia is often the earliest visible radiological
With MRI, a common finding in haemophilic arthropathy, subchondral cysts, can be identified and classified by their intensity into four categories [18]. In contrast, subchondral cysts are often missed on plain X-ray as a result of their positioning adjacent to osteopenic areas. Osteopenic areas produce juxta-articular radiolucent areas that obscure the cyst margins on plain X-ray [18]. Early detection of subchondral cysts with MRI supports local intervention to puncture the cyst with a trocar, aspirate the lesion and seal it with fibrin sealant or bone graft rather than waiting until the cyst is large and more extensive surgery is indicated.

There are four single case reports and two series demonstrating the value of MRI in visualizing haemophilic pseudotumours [19–24]. Jaovisidh et al. reported on 12 haemophilic pseudotumours and found MRI to be very accurate for localization of pseudotumour in fat, muscle, fascia, subperiosteum or bone [25]. Additionally, MRI is effective in delineating pseudotumour number, size, extent, neurovascular involvement and impact on surrounding structures. MRI findings can be used for treatment planning or to follow the course of pseudotumours.

With MRI, cartilage can be directly visualized in all compartments of a joint as an intermediate to high-intensity line next to the low-intensity subchondral bone [17]. In haemophilic arthropathy, cartilage may be directly destroyed, presumably secondary to exposure to blood products and the enzymes they attract or to the inflammatory changes associated with synovitis. In individuals with osteoarthritis, MRI has been shown to be better than plain X-ray in delineating joint patho-
Fig. 5.4 The T2-weighted coronal MRI view of both ankles shows subchondral cysts on the right (two arrows) and a large surface erosion on the left (three arrows). Cartilage loss is present in both ankles but more so in the left than right ankle. The large arrowhead points to synovial hyperplasia and haemosiderin deposition.

In an attempt to improve upon the capabilities of MRI in visualization of haemophilic arthropathy, Rand et al. [27] studied alternative imaging techniques. They concluded that MRI with three-dimensional gradient echo fat-suppression sequences was advantageous in allowing thin high-resolution contiguous slices with an increased signal:noise ratio to be obtained. This technique also supported high-quality image reformation. It was especially good for cartilage imaging because it increased the contrast: noise ratio between cartilage and joint fluid and between cartilage and subchondral bone. With Flash two-dimensional gradient echo imaging, a related technique, blood was appreciated in six joints that had no signs of haemorrhage by physical examination.

In attempting to optimize MRI evaluation of haemophilic arthropathy, a contrast agent, gadolinium has been administered intravenously. Gadolinium is a paramagnetic agent that acts to decrease the T1 but more so T2 relaxation time of tissue. Tissues enhancing with gadolinium appear brighter on T1-weighted images. The effect on T2-weighted images is minimal.

Nagele et al. [28] studied 17 haemophilic knees following intravenous gadolinium. They found synovial uptake of gadolinium was increased in haemophilic joints with only minimal uptake by muscle, fat, tendons, marrow or effusion. They concluded that gadolinium helped to delineate and quantify synovium. Rand et al. [27] gave gadolinium intravenously to 16 children with haemophilic arthropathy. They concluded that gadolinium helped to demarcate synovial hyperplasia from cartilage and fluid.

We and others (Bjorn Lundin, personal communication) have not found gadolinium to be of added value in imaging haemophilic arthropathy if gradient echo images are obtained.

Haemophilic arthropathy differs from other forms of arthritis because of the presence of haemosiderin deposits in much of the inflamed synovium. The presence of this low-signal substance is enhanced with gradient echo imaging. Disadvantages of gadolinium include added cost, the possibility of allergic reactions and the need for venous access which is often problematic, especially in young children.

Comparison studies of plain X-ray and MRI

Baunin et al. [15] reported on 28 haemophilic joints—17 knees, 10 ankles and 1 elbow—that were comparatively studied with plain X-ray and MRI. MRI revealed cartilage changes, effusions, synovial hyperplasia and early bone lesions better than plain X-ray. They concluded that MRI findings should be useful for developing treatment plans and monitoring response to treatment.

To date, the largest series of haemophilic joints (328 joints) comparatively studied by plain X-ray and MRI was reported by Briukhanov et al. in 1998 [29]. MRI was again reported to be superior in its ability to recognize haemarthroses and haemophilic arthropathy that was not appreciated by plain X-ray examination.

The most recent series evaluating MRI and haemophilic joints was published by Funk et al. in 2002 [30]. They compared 24 haemophilic joints evaluated by plain X-ray and MRI. The joints had at least one clinical manifestation of bleeding which was verified by ultrasonographic evaluation. There was good correlation between the number of joint haemorrhages and the MRI and Pettersson scores but MRI was superior in detecting early changes.
MRI findings and treatment planning

We postulated that MRI findings might globally effect management plans originally developed based on conventional plain radiographical data. We studied 14 target joints in 13 children with haemophilia, aged 7-16 years [31]. A target joint was defined as having sustained two or more haemorrhages per month in the preceding 6 months. After reviewing the history, examining the target joint and obtaining a plain X-ray of the target joint, a treatment plan was created. The MRI findings were then reviewed and resulted in a change in treatment plan in 40% of joint assessments.

In the Rand series, they compared the number of bleeding episodes, joint physical exam and pain scores, and plain X-ray findings with MRI assessments of 21 joints in 16 children [27]. They found the joint exam and pain scores underestimated joint changes identified with MRI. Similar to our study, based on MRI findings, the treatment plans were intensified for 40% of the children.

MRI and the impact of treatment interventions

We studied the preradiosynoviorthesis findings in 21 haemophilic joints by plain X-ray and MRI [32]. Synovial hyperplasia varied from small to large and did not affect the success rate of the procedure in reducing bleeding frequency. We found joint damage was underestimated by plain X-ray as compared with MRI prior to and 6 months following the injections. There was progressive joint damage in 28% of joints studied with MRI 6 months following the procedure. With MRI, progressive cartilage and bone damage could be appreciated in six of seven joints reimaged 1 and 2 years following the procedure. One joint had only synovial hyperplasia preprocedure, which diminished at follow-up.

We also studied the anatomical outcome in haemophilic joints at a median of 16 years postradiosynoviorthesis [33]. We studied 13 joints with extensive bone and cartilage loss, and found 11 joints had synovial hyperplasia on MRI. Both clinical examination and plain radiographs underestimated the presence of synovial hyperplasia and effusion compared with MRI.

MRI scale

We designed and published a provisional MRI scale for evaluation of haemophilic joints which is shown in Table 5.3 [33]. The haemophilic Denver MRI arthropathy scale was designed to be clinically practical to use but also effective for research trials. We modelled the scale after the Arnold and Hilgartner plain X-ray scale in that we made it progressive rather than additive. Information in each of the categories (effusion/haemarthrosis, synovial hyperplasia/haemosiderin, cysts/erosions and cartilage loss) is collected but the final score is the highest number or greatest degree of joint damage present. We chose complete loss of cartilage to represent the maximum damage because although bone cysts may be filled and erosions smoothed, cartilage repair is currently most difficult to achieve.

Soler et al. [34] published an alternative system for scoring haemophilic arthropathy based on MRI findings. Their scale ranges from 0 (no abnormalities) through grade I (minimal amount of haemosiderin), grade II (large amount of haemosiderin and isolated cartilaginous erosion), grade III (cartilage destruction, bone erosions and subchondral cysts) to grade IV (large internal joint derangement, secondary osteoarthritis and/or ankylosis).

Conclusions

In conclusion, there are strengths and weaknesses associated with plain X-ray, ultrasonography and MRI of haemophilic joints. However, MRI is superior to plain X-ray and ultrasound in visualizing synovial hyperplasia, early cysts and cartilage loss.

Acknowledgement

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References

Introduction

Ultrasonography (US) is an imaging technique with a progressive and extensive use in the musculoskeletal system. US has some potential advantages over other imaging modalities, including cost- and time-effectiveness, portability, real time and dynamic examinations, and a superior spatial resolution. In this way, US can be used as a first diagnostic imaging procedure instead of magnetic resonance imaging (MRI). The major disadvantage of US is its operator dependence, requiring a long learning curve. Moreover, most of the images achieved during US examination can only be interpreted accurately by the operator. Such operator-dependent performance and the limited value of images for orthopaedic surgeons and physicians may explain the initial resistance to demand this imaging technique and to prefer a more anatomical imaging modality, such as MRI. US is not very commonly used to detect haemophilic arthropathy, in spite of its potential capabilities [1]. There are only a few reports on US being used as a primary diagnostic imaging procedure in haemophilic patients and these studies have only reported on the haemophilic arthropathy changes in the knee [2,3]. Our group has recently reported on the utility of US in other haemophilic target joints, such as the elbow and ankle, compared with MRI [4].

Examination technique

A 7.5–12 MHz lineal transducer is usually used. A good understanding of anatomy is required to achieve spatial orientation and to identify the different anatomical structures. A brief description of the examination technique in the three most frequently involved joints in haemophilic patients is provided.

Knee

The patient is initially placed in the supine position with the knee flexed 45°. Examination starts in the longitudinal plane in the suprapatellar region, and images of the quadriceps tendon and suprapatellar recess are obtained in the longitudinal and transverse planes [5]. The suprapatellar bursa extends at least 5–6 cm above the patella and this is the best area in which to evaluate a possible synovial hypertrophy. With the knee flexed as much as possible, the anterior femoral cartilage is evaluated in the transverse plane. The examination continues with the patellar tendon, both medial and lateral aspects of the knee (meniscus, marginal bone and ligaments) and, finally, with the patient lying in the prone position, the posterior aspect of the knee is examined (condylar cartilage and synovium, Baker cyst and musculo-tendinous structures).

Elbow

The examination starts at the anterior elbow aspect, placing the transducer transversely on the humeral epiphysis. A smooth 1-mm band of hyaline cartilage is seen between the bone and the echogenic line of the capsule and periarticular fibrofatty tissue. Two longitudinal views are then performed, over the radiocapitellar and trochlea-ulna joints. From these positions, the transducer is shifted either medially or laterally to study the epitrochlear and epicondylar areas, respectively, including the collateral ligaments. Finally, the posterior aspect of the elbow is examined with the joint flexed 90° and with the palm resting on the table. In this position, the olecranon recess, the triceps tendon and muscle, and the ulnar nerve are explored [6].

Ankle

Examination starts with the patient in the supine position, the knee flexed and the foot in maximal plantar flexion. Images of the tibiotalar and talonavicular joints are obtained in the longitudinal plane [7]. The neck and the head of the talus are easy to identify, as well as the anterior tibialis and extensor tendons. The probe is then placed along the transverse plane and the cartilage of the anterior part of talus dome is assessed. For exploring the medial and lateral aspects of the ankle (and their ligaments and tendons) the patient’s limb is turned into the medial and lateral positions, respectively. Finally, the patient is turned into the prone position and the posterior tibiotalar joint is examined, as well as the Kager’s fat pad and the Achilles tendon.
Haemarthrosis

Haemarthrosis is defined as intra-articular bleeding. In most cases, clinical history and physical examination make the diagnosis obvious; however, if the diagnosis is in doubt, US can accurately confirm the clinical suspicion. The sonographic appearance of haemarthrosis depends on the evolution time, as is the case with haematomas. In acute cases, haemarthrosis is seen as a diffusely echogenic joint effusion with mobile internal echoes. As haemarthrosis evolves, the effusion becomes more hypoechoic and blood clots can be seen as echogenic nodular masses in a dependent position, which can sometimes be displaced with dynamic manoeuvres and/or probe compression. In chronic cases, a hypoechoic joint effusion is seen with some degree of synovial thickening. US is not able to distinguish haemarthrosis from infected fluid reliably and therefore clinical and analytical parameters are mandatory. If necessary, a joint aspiration can be safely performed with the patient under substitutive treatment.

Haemophilic synovium

The normal synovium is very thin and cannot be detected on US. When recurrent intra-articular bleeding occurs, the synovial membrane becomes thicker and the hypertrophied synovium is seen on US as a hypoechoic irregular band overlying the anechoic hyaline cartilage, or as a bulk of hypoechoic or mildly echogenic vegetations. In spite of the fact that US can easily distinguish between hypertrophied synovium and haemarthrosis effusion, there is sometimes difficulty in differentiating them. In such cases, a selective and gradual compression with the US probe may help to distinguish both entities; the fluid, when present, will be displaced out of the field of view, while the synovium, which rests between the joint capsule and the articular bone, remains incompressible (Fig. 6.1).

Within the knee, it is the suprapatellar pouch that has the best access for US, but medial and lateral compartments, as well as the posterior condylar area, can also be evaluated for hypertrophic synovium. In the elbow we use three planes for synovial measurements: transverse views over the humeral condyles and the olecranon recess, and a longitudinal view over the anterior radiohumeral joint. The best approach for evaluating the synovium in the ankle includes, in our opinion, two orthogonal planes over the anterior tibiotalar joint (with the foot in maximal plantar flexion) and two oblique planes over the medial and lateral aspects of the posterior mortise. At our institution, US combined with plain film has replaced MRI in most situations where hypertrophic synovium needs to be assessed.

Doppler US can be used to differentiate between active and inactive fibrous synovium. The former has increased flow signal at colour Doppler, while the latter has decreased or absent flow signal. Most studies with Doppler US evaluation of the synovium have been made in rheumatoid arthritis patients [8], and have shown a positive correlation between synovial hyperaemia and clinical parameters of active inflammation. This correlation has not been demonstrated in haemophilic patients, but our personal experience reveals that most haemophilic joints show minimal or absent flow signal, no matter what the degree of hypertrophy or the number of recurrent bleeding episodes. Increased flow signal can mainly be seen after an acute haemarthrosis episode or after radiosynoviorthesis and, when this occurs, hypertrophied synovium is mainly seen as a nodular, mildly echogenic structure (Fig. 6.2), very similar to the synovial pannus of rheumatoid arthritis [9]. Power Doppler has been demonstrated to be more sensitive for slow flow and
In spite of the capabilities of MRI, US cannot detect iron deposits in the synovial membrane. Some authors have proposed that early haemosiderin detection by MRI, when there is no clinical evidence of bleeding episodes, can help in the management of such haemophilic patients [12]. When US and MRI are compared, both techniques have shown a similar synovial thickening. Whenever haemosiderin was detected in MRI, some degree of synovial thickening was always present at US examination [4]. Moreover, US lacks the artefact seen on MRI when severe amounts of haemosiderin are present (Fig. 6.3), which makes the accurate measurement of the synovium difficult.

**Cartilage assessment**

US allows some degree of cartilage evaluation in those areas with acoustic window, such as the femoral trochlea and posterior condyles in the knee, the humeral condyles and head of the radius in the elbow, and the anterior surface of the talar dome in the ankle. Tight joints such as the hip are the most difficult to evaluate, whereas large and lax joints are better seen. A dynamic approach, with different manoeuvres, is best to explore the maximal extension of joint surface. In spite of its limited field of view, when compared with MRI, US is able to score the cartilage damage in a similar way to MRI [13]. However, US lacks the capability to explore the subchondral bone and the interosseous areas, but this limitation can be easily overcome when plain films are added.

The subchondral plate is seen on US as a regular, smooth and continuous hyperechoic line, covered by an anechoic, regular and smooth band of variable thickness, depending on the joint surface, relative to the hyaline cartilage. When joint effusion is present, the anechoic hyaline cartilage band is covered by a thin regular echogenic line representing the chondral surface. When cartilage degeneration, tear or loss are present, the hyperechoic cartilage band appears irregular and frayed. In addition, the subchondral plate appears irregular, and small holes can be seen representing subchondral cysts. As secondary osteoarthritis develops, articular bony edges become prominent and irregular and bony spurs or osteophytes are seen [14] (Fig. 6.4).

Attention must be taken when children are examined, because the hypoechoic epiphyseal cartilage should not be mistaken for hypertrophied synovium or haemarthrosis, especially when some degree of cartilage and subchondral plate damage is already present. In some instances, intra-articular loose bodies can be seen, such as chondral or osteochondral fragments. US shows these loose bodies as hyperechoic intra-articular areas with variable posterior shadowing. Demonstration of fluid surrounding the fragments, or their mobility with dynamic manoeuvres (including gentle compression with the probe), are definite diagnostic criteria [15]. Special attention must also be paid to any articular trauma in the haemophilic patient with a poor response to an adequate substitutive treatment, because the haemarthrosis can mask a radiographically occult fracture.
SONOGRAPHY OF HAEMOPHILIC JOINTS

In such cases, US can demonstrate a loose body representing an osteochondral fracture.

**Haematomas**

Haematomas are common complications after a minor trauma (or even spontaneous) in haemophilic patients. They can involve any organ or tissue in the body. The main locations and potential complications are beyond the scope of this chapter, but physicians should know that, in some instances, periarticular haematomas may be clinically interpreted as haemarthrosis. Those cases can be clearly depicted and correctly diagnosed on the basis of an US examination.

**Ligaments and tendons**

Ligaments and tendons are anisotropic structures and therefore are subjected to changes in echogenicity depending on the angle of incidence of the US beam. They must be studied with their longitudinal axis parallel to the probe, because artefactual hypoechogenicity caused by the obliquity of the angle of incidence of the US beam can lead to a false diagnosis of injury. If necessary, a gel stand-off pad can be used to permit steep probe angulation. Although ligament and tendon injuries are uncommon, we have recorded two cases of tenosynovitis in the ankle: one of them in the plantar course of the flexor hallucis longus (Fig. 6.5) (near Henry’s knot), and another case in the extensor digitorum longus, related to a communication with...
the talonavicular joint, which had a hypertrophic synovium. US examination was performed in both cases to evaluate a suspected hypertrophic synovium in the tibiotalar joint with a poor response to conservative treatment.

Bursae may be complicated with haemorrhage. When haemorrhagic bursitis occurs, the fluid effusion within the bursa shows internal echoes and the bursa walls may become thickened, such as in the articular synovium. As well as in the joint, with US it is not possible to differentiate this echogenic fluid from septic bursitis or microcristalline bursitis.

**Synoviorthesis**

Synoviorthesis has up to 86% success in controlling recurrent articular bleeding. However, its effects are quite variable in duration. In an attempt to evaluate if there was a relationship between the degree or severity of synovial hyperplasia and the clinical outcome of radiosynoviorthesis, Nuss et al. [16] performed both plain films and MRI studies in haemophilic patients before and after radiosynoviorthesis, and developed an MRI scale to grade the articular damage. Effusion, synovial hyperplasia, haemosiderin, bone erosions and cysts, and cartilage loss were the main parameters evaluated. In their study, the MRI scores did not have a predictive value in the clinical outcome after radiosynoviorthesis, with unchanged hypertrophic synovium thickness 6 months after radiosynoviorthesis, and with progressive articular worsening in later years as described prior with plain films. Interestingly, MRI was unable to differentiate active from inactive synovium, although the MRI studies were carried out without contrast enhancement. As expected, they concluded that MRI evaluation is not routinely indicated prior to radiosynoviorthesis. In spite of these limitations, clinicians are usually interested in knowing what the amount of synovium is before synoviorthesis, and what the response is after treatment. At our hospital, US is the preferred diagnostic imaging modality in such cases, because it is portable, inexpensive and, if necessary, may help to guide the joint puncture to avoid an extra-articular injection.

**Sonographic guidance for synoviorthesis**

Articular puncture in haemophilic patients can have two main purposes: to drain a haemarthrosis or to perform a synoviorthesis. The former is very controversial and is only performed in selected cases. Synoviorthesis is a widespread and well-recognized treatment for synovial hyperplasia [17,18]. The techniques of articular puncture for synoviorthesis have been well described by Rodriguez-Merchan and Goddard [19]. Although some complications have been reported secondary to the procedure, most of them are related to the extra-articular injection of the radionuclide [20,21], mainly in deep or complex joints (such as the hip, ankle or shoulder). US can accurately assess the intra-articular injection, both by planning the exact skin site of puncture and/or by direct visualization of the tip of the needle within the joint [22]. The US probe is placed over the selected pathway to reach the articular space. The plastic cup of the needle can be used to compress the skin, and this superficial movement can be registered with the US. The cup is displaced over the skin under US control to the selected point of injection, and the distance between the skin and the articular space is measured. Then, a heavier pressure is made with the cup to mark the skin. In most cases, the needle insertion can be performed without direct US control; the skin is sterilized with iodated alcohol and the needle is inserted through the skin mark with the same direction and angulation as the US probe, to the same depth as previously measured. A 23–25 gauge needle is usually used and no local anaesthesia is needed. Gently, aspiration is made to confirm the intra-articular position.

When an intra-articular needle position cannot be accurately demonstrated, there are two possibilities. The first is to perform a continuous controlled survey of the needle during insertion. The US probe is positioned near the needle and the tip of the needle should be visualized as a bright echoic dot or line (depending on the probe orientation) which is moved into the articular space (Fig. 6.6). If after this the needle tip is lost, which is possible in deep joints such as in the hip or shoulder (or when only minimal synovial hyperplasia is present), a small amount of air can be injected as an echogenic contrast [23]. If the needle is in an intra-articular position, the gas will outline the articular capsule. There is not necessarily a fixed pathway to puncature the joint, and the best approach may be selected in attention to a particularly enlarged synovial recess, such as in the posterior ankle, or in order to avoid a critical or a painful structure such as a tendon, vessel or nerve.
SONOGRAPHY OF HAEMOPHILIC JOINTS

Conclusions

US is a good diagnostic imaging modality in haemophilic patients. When an appropriate learning curve is achieved, US shows all its potentialities in the evaluation of haemophilic arthropathy, without any substantial discordance when compared with MRI. Moreover, US is a readily available, lower cost and bedside imaging technique, which also permits interventional guided procedures.

References

Introduction

Historically, empirical assessment was used to document the relative efficacy of treatment. This unscientific approach often resulted in erroneous conclusions by researchers, resulting from subjective interpretation of variables and the difficulty of evaluating results. Even the most conscientious researcher is subject to bias. The knowledge and perceptual ability of the examiner are important variables. Experienced examiners frequently produce differences when evaluating the limits of articular motion. The complexity of the joints and the number of criteria used to assess results make accurate evaluation even more difficult. This chapter analyses the orthopaedic assessment, the evolution and current structure of quality and outcome determination in health care and orthopaedics, the patient’s expectations, and health economics and orthopaedics.

Orthopaedic assessment

The method of grading and formatting data also influences the assessment. Values for a non-standardized category of variables are arbitrarily assigned a numerical score. Different interpretations of the relative value of the variables inevitably alter the evaluation. Currently, data collection formats include categorical assessment (excellent, good, fair and poor), numerical scoring (a total score or separate scores for subjective, objective and functional categories) and visual analogue scales. Comparisons of the relative success of different methods of treatment depends on the accurate evaluation of results. Assessment has been hindered by differences in the knowledge and perceptual abilities of the examiners, and in the different methods of grading and recording data. Under these circumstances, evaluation and comparison of different methods of treatment have been difficult.

Numerical scoring systems

The most widely used joint assessment instrument is the World Federation of Haemophilia (WFH) Physical Joint Examination instrument, which was developed 20 years ago by Pettersson and Gilbert [1] (Table 7.1). Recently, Manco-Johnson et al. [2] developed two expanded versions of the WFH instrument and a new instrument which they designed specifically with young children in mind. They called the revised instruments the Colorado physical examination (PE) instruments, full and half point (Colorado PE-1 and Colorado PE-0.5, respectively) (Tables 7.2 and 7.3), while the new instrument was termed the Child PE instrument (Table 7.4). Manco-Johnson et al. [2] reported that the WFH instrument is not adequately sensitive to be used as an evaluative instrument in children. The WFH instrument contains many tasks that cannot be performed by young children because of their developmental immaturity. The WFH instrument proved to be inadequate both for evaluation of children and for adults with mild haemophilic arthropathy.

There exists an urgent need for instruments that can detect mild differences in joint function. The instruments developed in Colorado by Manco-Johnson et al. [2] are better at discriminating severity of joint abnormality compared with the WFH instrument. The Colorado instruments should be further evaluated through use in prospective longitudinal randomized clinical trials in larger and younger populations. If future analyses validate the findings reported by Manco-Johnson et al. it may be reasonable to replace the WFH instrument with the Colorado PE-0.5 for children ≥ 7 years of age and the Child PE instrument for children aged 12 months to 6 years. However, there are a number of problems associated with numerical rating of symptoms. These problems are investigator bias, sensitivity, patient compliance and interpreter bias.

A visual analogue scale (VAS) solves many of the problems associated with describing the magnitude of subjective symptoms. A VAS consists of a line with the extremes of a given symptom at each end. The patient places a mark on the line to designate the level of symptoms relative to the extremes. The response can be converted to a numerical score by measurements. Some authors have found VASs to be superior to discontinuous verbal descriptors or numerical scores [3–6]. The VAS is easier to understand and therefore reduces investigator involvement and the introduction of bias. The VAS improves the analysis of symptoms by increasing patient compliance, enhancing sensitivity of measurement and reducing bias.
Quality and outcome determination in health care and orthopaedics

In orthopaedics, as in the rest of the health-care industry, there is currently a great deal of interest in, and activity related to, the definition and implementation of outcome measures. However, outcomes are only one aspect of quality in health-care delivery. The need to measure outcomes is simply part of an effort to quantify and then improve the quality of health care. Outcomes are quantifiable results that we should expect to achieve after treatment of the patient has been completed. Thus, the current quality triad includes practice guidelines, continuous quality improvement and outcome determination. A practice guideline or algorithm is a defined method of dealing with a clinical problem that seeks to minimize or eliminate the wide variations that may be seen when different approaches are taken to the same problem. In theory, the use of practice guidelines should improve outcomes.

Determination of outcome may be different from determination of quality. Outcomes are now more than the simple accounting of objective measures, such as morbidity, mortality and infection. An outcome is the patient’s health status subsequent to the application of a clinical process. It includes changes in physiology, symptoms, function and perception. Clinical experience has taught us that patients with excellent radiographs or good range of motion are not always satisfied with their outcome. Because impaired physical, social and emotional function may be the end result of many conditions, our evaluation of the outcome of treatment must take into account the patient’s overall health status, work ability, satisfaction, expectations and perception of pain. Today, throughout medicine, outcomes may include three basic types of information: 1 the traditional objective factors, such as strength or range of motion; 2 less objective determinations, such as function, health status, pain and satisfaction; and 3 an assessment of the value of the intervention.

Specific orthopaedic outcome tools

A vast array of validated outcome instruments are now available for the assessment of patients with musculoskeletal...
Table 7.2 Colorado physical examination (PE-1) full point instrument [2].

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Scale</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>0–3</td>
<td>0 = None; 1 = Joint looks slightly ‘puffy’, there is slight palpable swelling present; may not be any measurable difference between the joints; bony landmarks clearly visible; 2 = Joint looks swollen and the swollen area feels firm on palpation; may also feel boggy; there is measurable difference between the joints; bony landmarks are palpable but not visible; 3 = Joint and surrounding area look very swollen and are tense to palpation; there is a measurable difference between the joints and the bony landmarks are difficult to palpate</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>0–3</td>
<td>0 = None; 1 = Muscle has slightly less contour than the contralateral side; 2 = Flattening of the muscle belly; 3 = Severe muscle wasting and depression</td>
</tr>
<tr>
<td>Axial deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>0–2</td>
<td>0 = Normal; 0–7° valgus; 1 = 8–15° valgus or 1–5° varus; 2 = &gt; 15° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Ankle</td>
<td>0–2</td>
<td>0 = No deformity; 1 = Up to 10° varus or 1–5° varus; 2 = &gt; 10° valgus, or &gt; 5° varus</td>
</tr>
<tr>
<td>Crepitus with motion</td>
<td>0–3</td>
<td>0 = None; 1 = Barely detectable audible or palpable sensation during joint motion; 2 = More pronounced cracking and/or rough sensation during joint motion; 3 = Audible and palpable grinding and crunching during joint motion</td>
</tr>
<tr>
<td>Range of motion</td>
<td>0–3</td>
<td>0 = No loss; 1 = Loss of &lt; 10% of total FROM; 2 = Loss of 10–33% of total FROM; 3 = Loss of &gt; 33% of total FROM</td>
</tr>
<tr>
<td>Flexion contracture measured at hip, knee ankle and elbow</td>
<td>0–3</td>
<td>0 = Normal; 1 = 0–7°; 2 = 8–15°; 3 = &gt; 15°</td>
</tr>
<tr>
<td>Instability</td>
<td>0–2</td>
<td>0 = None; 1 = Present but does not interfere with function; 2 = Creates a functional deficit or requires bracing and orthosis</td>
</tr>
<tr>
<td>New additions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength against gravity</td>
<td>0–3</td>
<td>0 = Moves through FROM, takes maximal resistance; 1 = Moves through FROM, takes moderate resistance; 2 = Unable to move through FROM</td>
</tr>
<tr>
<td>Pain with activity</td>
<td>0–3</td>
<td>0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis; 1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic; 2 = Moderate pain, partial or occasional interference with occupation or activities of daily living; 3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics</td>
</tr>
<tr>
<td>Pain without activity</td>
<td>0–3</td>
<td>0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis; 1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic; 2 = Moderate pain, partial or occasional interference with occupation or activities of daily living; 3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics</td>
</tr>
<tr>
<td>Gait abnormalities*</td>
<td>0–3</td>
<td>0 = Normal walking, running, skipping, galloping, stairs; 1 = Normal walking, one or more other gait abnormality; 2 = Abnormal walking and 1 or 2 other gait abnormalities; 3 = Abnormal walking and 3 or more gait abnormalities</td>
</tr>
<tr>
<td>Total</td>
<td>0–31</td>
<td>(Ankle or knee); 0–29, elbow</td>
</tr>
</tbody>
</table>

FROM, full range of motion.

*Gait abnormalities include limping, walking with foot turned out, walking on side of foot, no push-off, walking on toes, uneven strides, no or uneven weight shifting, abnormal running, galloping, skipping or climbing stairs.
Table 7.3 Colorado PE-0.5: half point instrument [2].

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>0-2</td>
<td>0 = None&lt;br&gt;0.5 = Joint looks slightly 'puffy'; there is a slight palpable swelling present; may not be any measurable difference between the joints; bony landmarks clearly visible&lt;br&gt;1 = Joint looks swollen and the swollen area feels firm on palpation; may also feel boggy; there is measurable difference between the joints; bony landmarks are palpable but not visible&lt;br&gt;2 = Joint and surrounding area look markedly swollen and are tense to palpation; there is measurable difference between the joints and the bony landmarks are difficult to palpate</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>0-3</td>
<td>0 = None&lt;br&gt;0.5 = Muscle has slightly less contour than the contralateral side&lt;br&gt;1 = Flattening of the muscle belly&lt;br&gt;2 = Severe muscle wasting and depression</td>
</tr>
<tr>
<td>Axial deformity (Knee)</td>
<td>0-2</td>
<td>0 = Normal; 0-7° valgus&lt;br&gt;1 = 8-15° valgus or 1-5° varus&lt;br&gt;2 = &gt; 15° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Axial deformity (Ankle)</td>
<td>0-2</td>
<td>0 = No deformity&lt;br&gt;1 = Up to 10° valgus or 1-5° varus&lt;br&gt;2 = &gt; 10° valgus, or &gt; 5° varus</td>
</tr>
<tr>
<td>Crepitus with motion</td>
<td>0-2</td>
<td>0 = None&lt;br&gt;0.5 = Barely detectable audible or palpable sensation during joint motion&lt;br&gt;1 = More pronounced cracking and/or rough sensation during joint motion&lt;br&gt;2 = Audible and palpable grinding and crunching during joint motion</td>
</tr>
<tr>
<td>Range of motion</td>
<td>0-2</td>
<td>0 = No loss&lt;br&gt;0.5 = Loss of &lt; 10% of total FROM&lt;br&gt;1 = Loss of 10-33% of total FROM&lt;br&gt;2 = Loss of &gt; 33% of total FROM</td>
</tr>
<tr>
<td>Flexion contracture</td>
<td>0-2</td>
<td>0 = Normal&lt;br&gt;0.5 = 1-7°&lt;br&gt;1 = 8-15°&lt;br&gt;2 = &gt; 15°</td>
</tr>
<tr>
<td>Instability</td>
<td>0-2</td>
<td>0 = None&lt;br&gt;1 = Present but does not interfere with function&lt;br&gt;2 = Functional deficit or requires bracing and orthotics</td>
</tr>
<tr>
<td>New additions</td>
<td></td>
<td>0 = Moves through FROM, takes maximal resistance&lt;br&gt;0.5 = Moves through FROM, with moderate resistance&lt;br&gt;1 = Moves through FROM, cannot take resistance&lt;br&gt;2 = Unable to move through FROM</td>
</tr>
<tr>
<td>Pain with activity</td>
<td>0-3</td>
<td>0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis&lt;br&gt;1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic&lt;br&gt;2 = Moderate pain, partial or occasional interference with occupation or activities of daily living&lt;br&gt;3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics</td>
</tr>
<tr>
<td>Pain without activity</td>
<td>0-3</td>
<td>0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis&lt;br&gt;1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic&lt;br&gt;2 = Moderate pain, partial or occasional interference with occupation or activities of daily living&lt;br&gt;3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics</td>
</tr>
<tr>
<td>Gait abnormalities*</td>
<td>0-3</td>
<td>0 = Normal walking, running, skipping, galloping, stairs&lt;br&gt;1 = Normal walking, one or more other gait abnormality&lt;br&gt;2 = Abnormal walking and &lt; 2 other gait abnormalities&lt;br&gt;3 = Abnormal walking and &gt; 2 gait abnormalities</td>
</tr>
<tr>
<td>Total</td>
<td>0-25</td>
<td>Ankle or knee&lt;br&gt;0-23 Elbow</td>
</tr>
</tbody>
</table>

FROM, full range of motion.<br>*Limping, walking with foot turned out, walking on side of foot, no push-off, walking on toes, uneven strides, no or uneven weight shifting, abnormal running, galloping, skipping or climbing stairs.
Table 7.4 Child PE instrument [2].

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
</table>
| **Swelling**              | 0–3   | 0 = None  
|                           |       | 1 = Joint looks slightly 'puffy'; there is slight palpable swelling present; may not be any measurable difference between the joints; bony landmarks clearly visible  
|                           |       | 2 = Joint looks swollen and the swollen area feels firm on palpation; may also be feel boggy; there is measurable difference between the joints; bony landmarks are palpable but not visible  
|                           |       | 3 = Swollen and are tense to palpation; there is measurable difference between the joints and the bony landmarks are difficult to palpate  
| **Muscle atrophy**        | 0–3   | 0 = None  
|                           |       | 1 = Muscle has slightly less contour than the contralateral side  
|                           |       | 2 = Flattening of the muscle belly  
|                           |       | 3 = Severe muscle wasting and depression  
| **Axial deformity**       |       |                                               
| Knee                      | 0–2   | 0 = Normal; 0–7° valgus  
|                           |       | 1 = 8–15° valgus or 0–5° varus  
|                           |       | 2 = > 15° valgus or > 5° varus  
| Ankle                     | 0–2   | 0 = No deformity  
|                           |       | 1 = Up to 10° valgus or 1–5° varus  
|                           |       | 2 = > 10° valgus, or > 5° varus  
| **Crepitus with motion**  | 0–3   | 0 = None  
|                           |       | 1 = Barely detectable audible or palpable sensation during joint motion  
|                           |       | 2 = More pronounced cracking and/or rough sensation during joint motion  
|                           |       | 3 = Audible and palpable grinding and crunching during joint motion  
| **Range of motion**       | 0–3   | 0 = No loss  
|                           |       | 1 = Loss of < 10% of total FROM  
|                           |       | 2 = Loss of 10–33% of total FROM  
|                           |       | 3 = Loss of > 33% of total FROM  
| **Flexion contracture**   | 0–3   | 0 = Normal  
| (measured at hip, knee,   |       | 1 = 0–7°  
| ankle and elbow)          |       | 2 = 8–15°  
|                           |       | 3 = > 15°  
| **Instability**           |       | Deleted  
| **New additions**         |       |                                               
| **Pain with activity**    | 0–3   | Uses Faces Pain Rating Scale (Wong-Baker)  
|                           |       | 0 = Face is very happy  
|                           |       | 1 = Wong-Baker faces 1 & 2: hurts a little bit or a little bit more  
|                           |       | 2 = Wong-Baker face 3: hurts even more  
|                           |       | 3 = Wong-Baker faces 4 & 5: hurts a whole lot and as much as you can imagine  
| **Pain without activity** | 0–3   | Uses Faces Pain Rating Scale (Wong-Baker)  
|                           |       | 0 = Face is very happy  
|                           |       | 1 = Wong-Baker faces 1 & 2: hurts a little bit or a little bit more  
|                           |       | 2 = Wong-Baker face 3: hurts even more  
|                           |       | 3 = Wong-Baker faces 4 & 5: hurts a whole lot and as much as you can imagine  
| **Gait**                  | 0–3   | 0 = Normal walking, running, skipping, galloping, stairs  
|                           |       | 1 = Normal walking, one or more other gait abnormality  
|                           |       | 2 = Abnormal walking and < 2 other gait abnormalities  
|                           |       | 3 = Abnormal walking and > 2 gait abnormalities  
| **Strength**              | 0–3   | 0 = Moves easily through full ROM against gravity without observable/measurable atrophy and can take additional resistance  
|                           |       | 1 = Moves through available ROM, easily against gravity, may have observable/measurable atrophy and can take some additional muscle resistance  
|                           |       | 2 = Moves through full or available ROM against gravity, cannot take resistance  
|                           |       | 3 = Unable to move through full or available ROM against gravity because of weakness  
| **Splinting/orthotics**   | 0–3   | 0 = No use of splinting/orthotics  
|                           |       | 1 = Splinting/orthotic use required as needed after an acute haemarthrosis or for occasional support  
|                           |       | 2 = Splinting/orthotic use required regularly for high activity sports or to prevent recurrent haemarthrosis  
|                           |       | 3 = Splinting/orthotic use required continuously  
| **Total**                 | 0–31  | Ankle or knee  
|                           | 0–29  | Elbow  

FROM, full range of motion; ROM, range of motion.
conditions. Some instruments measure a patient’s general health status; others measure outcomes related to a specific anatomical region, body part or condition [7]. Validated measures of general health status such as the SF-36 Health Survey [8] and the Sickness Impact Profile [9], take into account various qualitative and quantitative facets of a person’s life; they do not refer to the specific disease or problem that is causing compromised health. One method by which general health status measures may be used in orthopaedics is to study the effect of a particular musculoskeletal condition on general health. General health measurement tools can also be used in orthopaedics to assess the effect of a treatment intervention on general health status.

Other types of instruments currently being used in musculoskeletal outcomes research are those that evaluate a specific organ system, body part or condition. The Musculoskeletal Function Assessment is an example of a validated instrument designed to measure outcome in regard to a specific organ system [10,11]. This instrument facilitates the evaluation of a wide range of musculoskeletal disorders and contains 10 categories (self-care, sleep/rest, hand/fine motor, mobility, housework, employment/work, leisure/recreation, family relationships, cognition/thinking, and emotional adjustment/coping/adaptation). This instrument has been shown to have good construct validity, content validity and reliability [10,11].

An example of a validated instrument that measures the outcome of treatment of a specific body part is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [12]. A number of other instruments and research techniques have been used for musculoskeletal outcome studies. Examples include the Brief Pain Inventory [13] and the Time Trade-off Technique [14]. The American Academy of Orthopaedic Surgeons (AAOS) has collaborated on a joint project with the individual specialty societies to produce the Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS; Table 7.5).

<table>
<thead>
<tr>
<th>Table 7.5 Questionnaires and modules contained in MODEMS [7].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb questionnaires</td>
</tr>
<tr>
<td>Foot and Ankle Questionnaire</td>
</tr>
<tr>
<td>Hip/Knee Questionnaire</td>
</tr>
<tr>
<td>Lower Limb Questionnaire</td>
</tr>
<tr>
<td>Sports Knee Questionnaire</td>
</tr>
<tr>
<td>Paediatric questionnaires</td>
</tr>
<tr>
<td>Paediatric Parent (child) Questionnaire</td>
</tr>
<tr>
<td>Paediatric Parent (adolescent) Questionnaire</td>
</tr>
<tr>
<td>Paediatric Adolescent Questionnaire</td>
</tr>
<tr>
<td>Upper limb (DASH, disabilities of the arm, shoulder and head)</td>
</tr>
<tr>
<td>questionnaire</td>
</tr>
<tr>
<td>Hip and knee module</td>
</tr>
<tr>
<td>Spine questionnaires</td>
</tr>
<tr>
<td>Cervical Spine Questionnaire</td>
</tr>
<tr>
<td>Lumbar Spine Questionnaire</td>
</tr>
<tr>
<td>Scoliosis Questionnaire</td>
</tr>
<tr>
<td>Patient satisfaction module</td>
</tr>
<tr>
<td>Employment module</td>
</tr>
<tr>
<td>Physician satisfaction module</td>
</tr>
</tbody>
</table>

Future of quality and outcomes research in health care

Quality determination and outcomes evaluation in health care are work in progress. The reliability, validity and accuracy of both processes, as well as outcome measures themselves, are constantly being re-evaluated and improved. The demand for continued development of practice guidelines and outcomes management on the basis of statistically validated studies of large populations will be emphasized both by individual specialty societies and by larger health-care organizations. In orthopaedics, it may signal an emphasis on the prevention of musculoskeletal disease. There is obviously much that remains to be done in this field. It is important that we, as practitioners, become involved in these new protocols, rather than having them mandated by outside agencies.

Patients’ expectations of knee surgery

Patients’ expectations of medical care are linked to their requests for treatment and to their assessments of outcome and satisfaction. Patients have multiple expectations of knee surgery in the areas of symptom relief and improvement of physical and psychological function, and these expectations vary according to the diagnosis. Mancuso et al. [15] developed two valid and reliable surveys that can be used preoperatively to direct patient education and shared decision-making, and to provide a framework for setting reasonable goals (Tables 7.6 and 7.7). Re-examining patients’ responses postoperatively could provide a way to assess fulfillment of expectations, which is a crucial patient-derived measure of outcome and satisfaction. There are several limitations to this study. First, the participants were all patients in a tertiary-care orthopaedic institution and therefore may not be representative of other patient populations. Secondly, some patients were interviewed in the hospital on the day of surgery, when their responses may have been affected by apprehension and anxiety. Thirdly, although the surveys were intended to be self-administered, they were tested during telephone and in-person interviews. This was done to maximize response rates during the test–retest phase.

Health economics and orthopaedics

Research that considers only the outcome and not the costs associated with the new technologies in health care is considered to be of limited value in making decisions about the use of scarce resources. Economic evaluation is becoming a standard feature of clinical research, but many published economic evaluations fall short of best practice in their methodology. Maniadakis and Gray [16] have described the essential features of economic evaluation, using published studies in orthopaedics, in order to try to improve the ability of orthopaedic surgeons...
Table 7.6 Hospital for Special Surgery knee surgery expectations survey [15]. (Mark an X on the number that best describes your response to each question.)

<table>
<thead>
<tr>
<th>How important are these expectations in the treatment for your knee?</th>
<th>Very important</th>
<th>Somewhat important</th>
<th>A little important</th>
<th>I do not expect this</th>
<th>This does not apply to me</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relieve pain: if you expect this, mark an X on one relieve some pain relieve most pain relieve all pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to walk: if you expect this, mark an X on one short distance (indoors, 1 block) medium distance (take a walk, less than 1 mile) long distance (more than 1 mile)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Increase knee stability</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Increase knee mobility</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to go up and down stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to squat</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to kneel</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stop knee from catching or buckling</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stop knee from giving way when coming to a quick stop while running</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stop knee stiffness or swelling</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Be employed for monetary reimbursement</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to run (for example, across the street, to catch the bus)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to perform daily activities (for example, daily routine, household chores)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to exercise or participate in sports: if you expect this, mark an X on what applies participate in recreational sports participate in professional sports</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Have confidence in knee</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Avoid future degeneration of knee</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to maintain general health</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve ability to interact with others (for example, take care of someone, play with children)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Improve psychological well-being</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>For knee to be back to the way it was before this problem started</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Outcomes may be measured in terms of both objective and subjective variables and also on the basis of cost-efficiency. Most tools currently used to quantify outcomes, especially in orthopaedics, involve measurements of general health and of specific body part or organ system function. Patients’ expectations of medical care are linked to their requests for treatment and to their assessments of outcome and satisfaction. Rating results are fundamental to evaluation and comparison of different methods of treatment. The discrepancies existing among rating scales have been an impediment in the evaluation of haemophilic patients from the orthopaedic point of view. Progress depends on international co-operation to improve communication and on the evaluation of new surgical techniques.

The WFH physical joint examination instrument and the Colorado PE instruments made important contributions by developing forms that will serve as a foundation for future evaluation systems. Some authors have suggested that the Colorado PE instruments are more indicative of early joint dysfunction.

Conclusions

Outcomes may be measured in terms of both objective and subjective variables and also on the basis of cost-efficiency.
Table 7.8 Summary of guidelines proposed by the US Panel on Cost-Effectiveness [16].

| Framework                                                                 | The background of the problem being addressed and the general design of the programme under investigation, including the target population, should be stated |
|                                                                         | The type of analysis to be performed should be clearly defined and justified |
|                                                                         | The comparator programme should be described |
|                                                                         | The perspective and the time horizon of the study should be stated |
| Data and methods                                                        | All resources of interest in the analysis should be clearly defined, measured and valued |
|                                                                         | All outcomes of interest should be clearly identified, measured and valued |
|                                                                         | Methods of obtaining estimates of effectiveness, costs and quality-of-life valuations and the sources of information should be given |
| Results                                                                 | The base case results in terms of costs, effectiveness and incremental cost-effectiveness ratios should be clearly set out |
|                                                                         | The sensitivity of the results and the assumptions and uncertainties should be reported |
| Discussion                                                              | The relevance of the study and policy questions and any ethical or distributive implications should be discussed |

than the WFH instrument. Future goals of the Colorado PE instruments are to refine the standard forms, identify additional important reproducible criteria and develop a comprehensive method of evaluation. It is paramount to develop valid and reliable surveys that can be used preoperatively to direct patient education and shared decision-making and to provide a framework for setting reasonable goals. Re-examining patients’ responses postoperatively could provide a way to assess...
fulfilment of expectations, which is a crucial patient-derived measure of outcome and satisfaction.

References

Introduction

Persons with haemophilia suffer recurrent episodes of haemorrhage into joints and muscles [1,2]. While intracranial and gastrointestinal haemorrhages are most often life-threatening, overall, musculoskeletal haemorrhages contribute the greatest long-term morbidity and cost to haemophilia. Accordingly, a primary goal of haemophilia therapy is to prevent or ameliorate damage to the musculoskeletal system. It was recognized early that an objective assessment of the structure and function of the musculoskeletal system for persons with haemophilia was critical to describe the natural history of recurrent bleeding into joints and evaluate the efficacy of various treatment interventions. The Pettersson score was developed using plain X-ray evaluation to stage and follow joint damage in persons with haemophilia [3]. The Pettersson scale has shown positive correlation with severity of haemophilia, duration of disease and number of haemarthroses [4,5]. Although plain X-ray is widely available and scoring the Pettersson scale is reproducible [6], X-ray evaluation is limited by lack of acceptance of radiation exposure for routine screening, particularly in children. In addition, the Pettersson scale frequently lacks correlation with important clinical outcomes as exercise and physiotherapy are able to maintain or restore function in anatomically damaged joints [7].

Range of motion has been the most commonly used single physical examination outcome measure to evaluate infusion regimens and surgical procedures [8–13]. Range of motion alone, however, is not sufficient to assess joint function and omits critical information such as muscle strength and bulk or evidence of synovitis. Muscle strength has been studied as an outcome indicator of recurrent joint haemorrhage [14] but has not been adopted as a single measure. As multiple medical and surgical approaches were developed, an instrument was required to compare physical outcomes across different populations of persons with haemophilia. With this purpose in mind, the World Federation of Haemophilia (WFH) adopted the Physical Examination (PE) Scale [15], which had been developed and used for over 25 years to determine and follow joint outcome [16–21]. The WFH PE scale was constructed to compare a very broad range of physical abnormalities across multiple cultures that had widely variable resources to treat musculoskeletal haemorrhages in person with haemophilia. Because of the breadth of the scale, young children with very different physical findings can receive the same score on the WFH PE scale, limiting its usefulness to discriminate mild to moderate degrees of abnormalities. More recently, with the development of highly efficacious intensive treatment regimens for the prevention of haemorrhage in persons with haemophilia, there have evolved more sophisticated requirements for a very sensitive physical assessment tool. This tool must now detect the earliest evidence of joint damage in order to direct optimal medical care and must also detect more modest differences in outcome between different clinical regimens for application to prospective randomized clinical trials.

Information obtained from a physical joint examination

Prior to the availability of replacement therapy to cease bleeding episodes, the focus of the physical assessment was primarily to describe and catalogue the acute and chronic changes in musculoskeletal structure and function secondary to haemorrhage.

There are two primary types of evidence that may be derived from a physical limb assessment: evidence for acute bleeding and evidence for chronic degenerative changes caused by recurrent bleeding episodes. The signs and symptoms of acute bleeding relate to distension of the joint capsule by blood. Joint haemorrhage, if untreated at its earliest onset, causes findings beginning with subjective symptoms of tingling, stiffness, fullness and pain progressing to objective signs of swelling, decreased range of motion and warmth. Chronic degenerative changes resulting from joint haemorrhage are both structural and functional. Structurally, synovitis, with palpable thickening of the joint lining, is often the first sign of chronic joint haemorrhage in young children. On histological examination, haemosiderin deposition is detected in hypertrophied synovium leading to tissue damage [22,23]. Magnetic resonance imaging (MRI) of chronically thickened haemophilic joints reveals soft-tissue signs of synovial hypertrophy with haemosiderin deposition with or without the presence of blood or effusion [24–26]. Functionally, over time the joint shows decreased range of

45
motion and, as a consequence of diminished use, the affected limb exhibits decreased muscle mass and strength. Physical evidence of structural joint damage is usually delayed beyond the earliest functional deficits and includes bony overgrowth, crepitus, fixed contractures and pathological angulation. Pathologically, haemophilic arthropathy resembles degenerative osteoarthropathy with subchondral cyst formation and erosion of cartilage [27]. Ultimately, bony sclerosis and spontaneous joint fusion occur. The physical assessment tool of the physiotherapist or orthopaedist must be able to assist the patient and his family to determine whether an acute bleeding event is present and must also be able to document signs of chronic changes related to recurrent joint haemorrhage as these changes impact function and structure of the limb.

**History of the WFH PE scale**

When the WHF PE scale was adopted and recommended for routine use in haemophilia clinics, most persons with haemophilia had no access to factor VIII replacement therapy for acute bleeding events. Even fewer persons were receiving routine infusions to prevent episodes of joint haemorrhage. Therapy for acute bleeding events comprised joint rest, ice, compression and elevation. Physical therapy was a mainstay of treatment for each episode of haemorrhage, and short-term joint splinting was employed by many haemophilia clinics. Factor replacement, where available, was administered in lower dosage and fewer infusions, compared with current standards [8]. Consequently, restricted joint motion with secondary effects on soft tissues developed in most persons with severe haemophilia. The Orthopaedic Outcome Study, conducted in six countries, found that 90% of persons with haemophilia between the ages of 6 and 31 years had abnormalities in 1–6 index joints using plain X-ray and the WFH PE scale to detect joint abnormalities [28].

Orthopaedic interventions were developed to deal with progressive joint destruction and included open synovectomy, joint fusion (arthrodesis) and joint replacement (arthroplasty) and later arthroscopic synovectomy and radiofrequency ablation. Physical therapy was vigorously applied to reversible abnormalities. The effect of orthopaedic surgical interventions and physical rehabilitation have been documented and followed using the WFH PE and other physical joint assessment scales [18–20,29,30]. Later, the outcome of persons using routine infusions of clotting factor concentrate to prevent joint damage was documented and prospectively followed using annual assessments with the WFH PE scale [16,17,21,28,31,32].

**Design and use of a joint physical examination instrument**

There are multiple uses for a joint physical examination instrument. In the design of a practical tool the various purposes of the assessment tool must be considered, as follows.

1. **Serial assessment of individuals and populations over time.** As an annual assessment tool, the PE scale is used to follow individuals over time. Attention is paid especially to evidence for development of a target joint and subsequent loss of function. Important physical findings include chronic joint swelling, asymmetry in muscle bulk and strength suggesting atrophy and decreased range of motion. Fixed contractures, angulation and severe crepitus are late findings. Changes across a population over time can be used to document progressive joint deterioration with age and recurrent haemorrhages, or improved outcomes with newer therapeutic interventions.
2. **Assessment following a severe joint or muscle haemorrhage and documentation of full recovery.** Following an acute haemorrhage, a comprehensive physical examination is important to document complete resolution of a haematoma or haemarthrosis, with restoration of range of motion and preservation or recovery of muscle strength and bulk.
3. **To guide postoperative rehabilitation and assess the outcome of surgical procedures.** Orthopaedic surgical interventions are usually performed to decrease the frequency of bleeding into a joint or to reduce pain. Surgical procedures, per se, rarely result in improved joint motion or function. Surgical inflammation, along with postoperative correction of factor deficiency, fosters formation of fibrous adhesions and loss of joint motion. A comprehensive physiotherapy evaluation is required prior to joint surgery. Perioperative physical therapy must be carefully planned and executed to maintain existing motion and strength and occasionally exceed baseline values.
4. **Application to outcome assessment in randomized clinical trials.** There have been few controlled studies of haemophilia therapies. Consequently, there is a dearth of evidence-based treatment guidelines for musculoskeletal haemorrhages in persons with haemophilia. Most treatment studies have consisted of open-label trials and have employed subjective short-term self-assessment of haemostasis with no objective outcome measure. A sensitive, specific, validated physical examination tool would facilitate a meaningful outcome assessment of the efficacy of therapies to prevent joint damage.

**Evidence that a more sensitive physical examination instrument is needed for children**

As the goal of haemophilia therapy shifted from restoration of musculoskeletal damage to prevention of joint disease, interest in physical assessment of very young children has become increasingly important. The primary elements of the physical examination of a joint have not changed since the development of the WFH PE Scale. Examinations must include assessments of muscle strength and atrophy, joint swelling and range of motion, and pain.

It became apparent to physical therapists, physicians and nurses working in paediatric haemophilia treatment centres that several items of the WFH PE scale are inappropriate for
Elements of a physical joint assessment tool and comparison of three existing scales

Key elements of the physical examination of a joint include swelling, range of motion, contractures, crepitus, angulation, instability and pain. Muscle evaluation includes assessments of atrophy and strength. The WFH PE scale is displayed in Table 8.1(a) and the WFH pain scale is displayed in Table 8.1(b). A perfect joint is scored as 0. Swelling of the joint capsule is rated as absent or present. A qualitative designation, ‘S’, indicates the palpable presence of thickened inflamed synovium. Crepitus, a rough palpable sensation and/or sound elicited on joint motion, is rated as absent or present. The range of motion of the joint is scored by percentage loss of normal full range of motion. The presence of a fixed flexion contracture earns an additional score. Atrophy of the muscles supporting the joint is scored as absent or present. Instability of the joint is scaled for presence as well as accompanying functional deficits. Finally, axial deformity is assessed for the knee and ankle only. Scores for all of the items contribute to the total scale independent of each other, making this an additive scale. In the original reports of haemophilia outcomes using various treatment regimens, the score for each of the six index joints, including both elbows, knees and ankles, were added together. A maximum score for one joint was 12 for the knee and ankle and 10 for the elbow, giving a total body maximum of 68 points.

In order to accommodate developmental changes, a scale was developed to be more sensitive and specific for the assessment of young children with haemophilia. This scale, the Colorado Young Child Scale (CYC), has been previously published and is shown in Table 8.2 [34]. The CYC defined swelling, muscle atrophy and range of motion in children and expanded the scores to three gradations of abnormality. Instability, angulation and crepitus were deleted. The Wong–Baker pain scale was incorporated into the physical assessment [35]. Strength and use of splinting devices or orthotics were added to the scale with three gradations of abnormalities defined. Activities to test strength in children who are too young to perform a break test were added; examples are shown in Table 8.3. Gait assessment was added. A perfect joint score is 0. A maximum joint score is 28 for the knee and ankle and 26 for the elbow, yielding a combined maximal total of 164.

A scale for older children and adults was developed from a modification of the WFH PE Scale, as shown in Table 8.4. The Colorado Adolescent/Adult ‘Half-Point’ Scale was so-named because mild degrees of abnormality were given less weight than moderate and severe degrees. A normal joint is scored 0 as in the WFH PE scale. Maximal joint scores are 24 for the knee and ankle and 22 for the elbow, giving a potential combined maximum of 140. The Colorado Adolescent/Adult Half-Point Scale differs from the CYC Scale by the exclusion of orthotics as a scored item, the retention of crepitus and instability and the use of a pain scale more appropriate for adults. The Colorado Adolescent/Adult Half-Point and Young Child scales were applied to an analysis of joint assessment preceding and following radiosynoviorthesis and found to have better correlation with the WFH pain scale than either the WFH PE scale or a uniformly weighted version of the Colorado Adolescent/Adult scale [34]. The CYC and Half-Point Adolescent/Adult scales are currently undergoing formal validation. Further refinement may be necessary based on the outcomes of these studies.

Swelling

Swelling is assessed by visual inspection and palpation of the joint in reference to anatomical landmarks as well as in
### Physical joint examination recommended by the orthopaedic advisory committee of the World Federation of Haemophilia (WFH) [15].

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Swelling</strong></td>
<td></td>
<td>0 = None, (S) if chronic synovitis is present</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>0–1</td>
<td>0 = ≤ 1 cm, 1 = Present</td>
</tr>
<tr>
<td>Axial deformity: measured at knee and ankle only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>0–2</td>
<td>0 = 0–7° valgus, 1 = 8–15° valgus or 0–5° varus, 2 = &gt; 15° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Ankle</td>
<td>0–2</td>
<td>0 = No deformity, 1 = ≤ 10° valgus or ≤ 5° varus, 2 = &gt; 10° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Crepitus on motion</td>
<td>0–1</td>
<td>0 = None, 1 = Present</td>
</tr>
<tr>
<td>Range of motion</td>
<td>0–2</td>
<td>0 = Loss of &lt; 10% of total FROM, 1 = Loss of 10–33 1/3% of total FROM, 2 = Loss of &gt; 33 1/3% of total FROM</td>
</tr>
<tr>
<td>Fixed contracture</td>
<td>0 or 2</td>
<td>0 = &lt; 15% fixed flexion contracture at hip or knee or equinus at ankle, 2 = ≥ 15% fixed flexion contracture at hip or knee or equinus at ankle</td>
</tr>
<tr>
<td>Instability</td>
<td>0–2</td>
<td>0 = None, 1 = Present but neither interferes with function nor requires bracing, 2 = Instability that creates a functional deficit or requires bracing</td>
</tr>
</tbody>
</table>

Total score: 0–12
- Ankle or knee
- Elbow

FROM, full range of motion.

### Pain instrument recommended by the orthopaedic advisory committee of the WFH [5].

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>0–3</td>
<td>0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis, 1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic, 2 = Moderate pain, partial or occasional interference with occupation or activities of daily living, 3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic medications</td>
</tr>
</tbody>
</table>

Comparison with the contralateral joint. The observer first inspects joint pairs to detect gross differences. Circumferential measurements can be used to record swelling if the landmarks are not visible. In less severe swelling, bony landmarks can still be determined; therefore circumferential measurement may not provide much information. When measuring the circumference of a joint it is important to document exactly where the measurement was taken in reference to a landmark so the measurement can be reliably compared with a future determination or that of another observer. Swelling can graded as mild, moderate or severe as shown in Table 8.2. Swelling as a result of synovial thickening may be appreciated by an experienced examiner by palpation of a tissue rather than fluid density.

### Range of motion

Range of motion is measured using a goniometer. Scores can be compared utilizing the average range of motion scales in Norkin and White’s *Measurement of Joint Motion: A Guide to Goniometry* [36]. The Norkin and White textbook contains standards to which measurements can be compared, including those recommended by the American Academy of Orthopaedic
### Table 8.2 Colorado Young Child instrument.

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Swelling</strong></td>
<td>0–3</td>
<td>0 = None 1 = Joint looks slightly 'puffy'; there is slight palpable swelling present; may not be any measurable difference between the joints; bony landmarks clearly visible 2 = Joint looks swollen and the swollen area feels firm on palpation; may also feel boggy; there is measurable difference between the joints; bony landmarks are palpable but not visible 3 = Swollen and are tense to palpation; there is measurable difference between the joints and the bony landmarks are difficult to palpate</td>
</tr>
<tr>
<td><strong>Muscle atrophy</strong></td>
<td>0–3</td>
<td>0 = None 1 = Muscle has slightly less contour than the contralateral side 2 = Flattening of the muscle belly 3 = Severe muscle wasting and depression</td>
</tr>
<tr>
<td><strong>Axial deformity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>0–2</td>
<td>0 = Normal; 1–7° valgus 1 = 8–15° valgus or 0–5° varus 2 = &gt; 15° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Ankle</td>
<td>0–2</td>
<td>0 = No deformity 1 = Up to 10° valgus or 1–5° varus 2 = &gt; 10° valgus, or &gt; 5° varus</td>
</tr>
<tr>
<td><strong>Range of motion</strong></td>
<td>0–3</td>
<td>0 = No loss 1 = Loss of &lt; 10% of total FROM 2 = Loss of 10–33% of total FROM 3 = Loss of &gt; 33% of total FROM</td>
</tr>
<tr>
<td>Contracture: measured at</td>
<td>0–3</td>
<td>0 = Normal 1 = 1–7° 2 = 8–15° 3 = &gt; 15°</td>
</tr>
<tr>
<td>knee, ankle and elbow</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0–3</td>
<td>0 = Moves easily through full ROM against gravity without observable/measurable atrophy and can take additional resistance 1 = Moves through full or available ROM easily against gravity, may have observable/measurable atrophy and can take some additional muscle resistance 2 = Moves through full or available ROM against gravity, cannot take resistance 3 = Unable to move through full or available ROM against gravity as a result of weakness</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
<td>0–2</td>
<td>0 = Normal walking, running, skipping, galloping, stairs 1 = Normal walking, at least one gait abnormality, e.g. foot turned out, shortened stance phase, no heel-toe pattern, decreased push-off, toe walking, etc. 2 = Abnormal walking and abnormal higher skills</td>
</tr>
</tbody>
</table>

The components of gait that should be assessed in each of the above skills are:

**Ankle**  
1. Equal weight shift  
2. Heel–toe pattern  
3. Good plantar flexion push-off  
4. Steps of equal length  
5. Steps of equal cadence  
6. Toes pointed symmetrically forward

**Knee**  
1. Equal weight shift  
2. Heel strike with full knee extension  
3. Good knee extension on push-off  
4. Steps of equal length  
5. Steps of equal cadence  
6. Toes pointed symmetrically forward

**Splinting/orthotics**  
0–3  
0 = No use of splinting/orthotics  
1 = Splinting/orthotic use required as needed after an acute haemarthrosis or for occasional support  
2 = Splinting/orthotic use required regularly for high-activity sports or to prevent recurrent haemarthrosis  
3 = Splinting/orthotic use required continuously

**Pain with activity**  
0–3  
0 = Face is very happy  
1 = Wong-Baker faces 1 & 2: hurts a little bit or a little bit more
Surgeons. In recording range of motion it is important to be consistent in patient positioning and to have adjacent muscle groups in a relaxed non-stretched position. The examiner aims to determine the maximal possible movement of the joint, without interference resulting from muscle tightness. Positioning should be recorded and all future measurements should be determined in this position for comparability. Active range of motion is elicited by asking the patient to extend or flex his joint fully, while passive range of motion is elicited by non-forceful guidance of a joint through available range by the examiner. Both of these ranges should be noted.

The two Colorado scales record actual range of motion, including hyperextensibility, if present, and reference future range of motion to this baseline.

### Fixed contracture

A joint with a fixed contracture cannot be moved through full range of motion with either active or passive manipulation.

### Crepitus

Crepitus is an audible and/or palpable sensation of roughness, popping, rubbing or cracking during active or passive joint motion. Crepitus has been scored as mild to severe as shown in Table 8.4.

### Angulation

Angulation is defined as the degree of variation in the joint from the midline of the body. Angulation is assessed by observation and measurement of the knee and ankle in a weight-bearing position. Terms used to describe this deformity are varus (angulation of the part distal to the joint towards the midline, ‘bow-legged’) and valgus (angulation of the part distal to the joint away from the midline, ‘knock-kneed’). Measurements are taken using a goniometer. The knee should be measured from the front. One arm of the goniometer is aligned along the shaft of the femur and the other arm is aligned along the shaft of the tibia with the axis at the knee. The ankle should be measured from behind by first bisecting the calcaneus, then aligning one of the arms of the goniometer with the line of the tibia and the other arm with the line bisecting the calcaneus. Angulation measurements change physiologically between 1 and 3 years of age and for this reason were excluded from the CYC scale.

### Instability

Instability occurs with advanced joint disease when ligamentous and capsular supports are weakened or eroded. Instability has been graded using two grades of severity as shown in Table 8.1(a) (WFHPE scale).

### Atrophy

Atrophy is defined as the reduction in size or wasting of a muscle. Because individual extremities vary in length and bony structure, not all muscles can be measured at the exact same point. However, within an individual, an atrophied muscle can be measured and compared to its contralateral counterpart. If the contralateral limb is normal, then difference in circumference measurement can reflect the presence of atrophy. However, if both sides are abnormal, then visual assessment is a helpful adjunct. Table 8.2 displays visual markers to assess the degrees of atrophy.

### Strength

Strength is defined as ability of muscles to move through full or available range of motion against gravity with or without additional resistance. Decreased strength is graded as mild to severe as described in Table 8.2. Children under the age of 4 years are unable to perform a strength break test. Instead, young children should be tested functionally using developmentally appropriate
Table 8.3 Functional muscle strength testing in young children. For children less than 4 years, the following functional tests can be used to estimate muscle strength. Have the child perform three repetitions of each movement.

Knee flexion: choose one of the following two tests
- Functional test for knee flexion: squats, three repetitions—use on ages 1 and 2 years. Have the child squat down to pick up a toy up from the floor and hold it for 5 s
- Resisted kicking, three repetitions—ages 1 and 2 years. If the child is actively protesting and doing some kicking during the evaluation, you may be able to resist his flexion movement. You may elicit the kicking by tickling the bottom of the child's feet

Knee extension: choose one of the following two tests
- Alternate functional test for knee extension strength: half-kneel to stand position (three repetitions)—can be used on all ages. Start the child in kneeling position. Encourage him to move into the half-kneel and on up to the standing position doing each one three times on each leg. Child should be able to control the movement into standing. Do not let him push on his hand although he can hold on to something for balance. You may need to help facilitate the movement as many children have a preference for only doing the movement on one leg. Facilitate him into half-kneel and encourage him to stand independently
- Functional test for extension strength: stair climbing
  (a) 18 months Climb 4 steps, step-to-position
  (b) 24–36 months Climb 4 steps, foot-over-foot with support
  (c) Over 3 years Climb 4 steps, foot-over-foot with no support
As you are evaluating stair climbing, note with which leg the child prefers to ascend and also with which leg he prefers to descend the stairs. Try to do three repetitions on each leg in both ascending and descending

Ankle dorsiflexion: choose one of the following two tests
- Functional test for strength: heel walking or tip child backwards off balance (weight on his heels) to get a righting reaction (three repetitions)—ages 3 years and up. Have the child walk 10 feet (3 metres) across the floor in a heel-walking position, or you can try tipping him off balance backwards to elicit a righting reaction
- Alternate functional test: resisted dorsiflexion, 'Tickle Test'—ages 1–2 years. If the child cannot co-operate with heel-walking because of his age you may be able to get some resisted dorsiflexion while tickling the bottom of his foot. As he wiggles to get away from the tickling, resist his dorsiflexion at the same time

Ankle plantar flexion: choose one of the following two tests
- Functional test for strength: toe walking for 10 feet (3 metres), three times—can be used on ages 2 years and up. Try to get the child to emulate you by walking 10 feet (3 metres) across the room on his toes
- Alternate functional test for strength: reaching for toy while going up on toes—can be used on ages 1 year and up. Have the child reach up high for a toy or a ball so that he must go on his toes to reach the object. It is helpful to have him standing very close to a wall (facing it.) That way he can use his free arm to support himself and keep from falling as he reaches for the ball

Elbow flexion: choose one of the following two tests
- Functional test for strength: lifting a book or weighted toy against gravity (three repetitions). Have the child pick up a book or weighted toy (1–2 pounds (0.5–1.0 kg)) and, with the elbow in the flexed position, carry it 10 feet (3 metres) across the room. He should repeat this three times with each arm. (A small toy purse works well for this test.) Use a 1 lb (0.5 kg) weight for ages 1–2 years. Use a 2 lb (1 kg) weight for ages 3–4 years
- Alternate functional test: pulling to sit from supine—use on ages 1–2 years. A very young child frequently will not follow the orders to bring the object to you. If this becomes a problem, you can try pulling him to sit from the supine position at least three times

Elbow extension: choose one of the following tests
- Functional test for strength: wall push-ups—can be used on ages 4 years and up. Have the child lean into the wall and do 10 push-ups
- Functional test for strength: wheelbarrow walk—can be used on ages 1–4 years. Hold the child under the lower abdomen and have him wheelbarrow walk 10 feet (3 metres) three times
- Functional test for strength: crawling—can be used in children 6–18 months. Have child crawl for 10 feet (3 metres) three times and observe how elbow extensors function

Forearm supination: perform the following test
- Supination functional test for forearm—can be used on ages 2–4 years. Use 1 lb (0.5 kg) weight for 1- and 2-year-olds. 2 lb (1 kg) weight for 3- and 4-year-olds. With the elbow in at his side flexed to 90°, have the child hold the weight with the palm down. Ask the child to turn the palm up while holding the weight. Repeat three times

Forearm pronation: perform the following test
- Functional test for forearm pronation—can be used on ages 2–4 years. Use 1 lb (0.5 kg) weight for 1- and 2-year-olds. 2 lb (1 kg) weight for 3- and 4-year-olds. With the elbow in at his side flexed to 90°, have the child hold the weight with the palm up. Ask the child to turn the palm down while holding the weight. Repeat three times
### Table 8.4 Colorado ‘Half-Point’ Scale.

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>0–2</td>
<td>0 = None 0.5 = Joint looks slightly ‘puffy’; there is slight palpable swelling present; may not be any measurable difference between the joints; bony landmarks clearly visible 1 = Joint looks swollen and the swollen area feels firm on palpation; may also feel measurable difference between the joints; bony landmarks are palpable but not visible 2 = Joint and surrounding area look markedly swollen and are tense to palpation; there is measurable difference between the joints and the bony landmarks are difficult to palpate</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>0–2</td>
<td>0 = None 0.5 = Muscle has slightly less contour than the contralateral side 1 = Flattening of the muscle belly 2 = Severe muscle wasting and depression</td>
</tr>
<tr>
<td>Axial deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>0–2</td>
<td>0 = Normal; 0–7° valgus 1 = 8–15° valgus or 1–5° varus 2 = &gt; 15° valgus or &gt; 5° varus</td>
</tr>
<tr>
<td>Ankle</td>
<td>0–2</td>
<td>0 = No deformity 1 = Up to 10° valgus or 1–5° varus 2 = &gt; 10° valgus, or &gt; 5° varus</td>
</tr>
<tr>
<td>Crepitus with motion</td>
<td>0–2</td>
<td>0 = None 0.5 = Barely detectable audible or palpable sensation during joint motion 1 = More pronounced cracking and/or rough sensation during joint motion 2 = Audible and palpable grinding and crunching during joint motion</td>
</tr>
<tr>
<td>Range of motion</td>
<td>0–2</td>
<td>0 = No loss 0.5 = Loss of &lt; 10% of total FROM 1 = Loss of 10–33% of total FROM 2 = Loss of &gt; 33% of total FROM</td>
</tr>
<tr>
<td>Contracture</td>
<td>0–2</td>
<td>0 = Normal 0.5 = 1–7° 1 = 8–15° 2 = &gt; 15°</td>
</tr>
<tr>
<td>Instability</td>
<td>0–2</td>
<td>0 = None 1 = Present but does not interfere with function 2 = Functional deficit or requires bracing + orthotics</td>
</tr>
<tr>
<td>Strength against gravity</td>
<td>0–2</td>
<td>0 = Moves easily through full ROM against gravity without observable/measurable atrophy and can take additional resistance 0.5 = Moves through full or available ROM easily against gravity, may have observable/measurable atrophy and can take some additional muscle resistance 1 = Moves through full ROM, cannot take resistance 2 = Unable to move through full or available ROM against gravity because of weakness</td>
</tr>
<tr>
<td>Gait abnormalities*</td>
<td>0–2</td>
<td>0 = Normal walking, running, skipping, galloping, stairs 1 = Normal walking, at least one gait abnormality, e.g. foot turned out, shortened stance phase, no heel–toe pattern, decreased push-off, toe walking, etc. 2 = Abnormal walking and abnormal higher skills</td>
</tr>
</tbody>
</table>

The components of gait that should be watched for in each of the above skills are:

- **Ankle**
  1. Equal weight shift
  2. Heel–toe pattern
  3. Good plantarflexion push-off
  4. Steps of equal length
  5. Steps of equal cadence
  6. Toes pointed symmetrically forward

- **Knee**
  1. Equal weight shift
  2. Heel strike with full knee extension
  3. Good knee extension on push-off
  4. Steps of equal length
  5. Steps of equal cadence
  6. Toes pointed symmetrically forward
Table 8.4 (cont’d)

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
<th>Scoring key</th>
</tr>
</thead>
</table>
| Pain with activity        | 0-3   | 0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis  
1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic  
2 = Moderate pain, partial or occasional interference with occupation or activities of daily living. May require more regular non-narcotic analgesia  
3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics |
| Pain without activity     | 0-3   | 0 = No pain, no functional deficit, no analgesic use except with acute haemarthrosis  
1 = Mild pain, does not interfere with occupation nor with activities of daily living; may require occasional non-narcotic analgesic  
2 = Moderate pain, partial or occasional interference with occupation or activities of daily living. May require more regular non-narcotic analgesia  
3 = Severe pain, interferes with occupation or activities of daily living, requires frequent use of non-narcotic and narcotic analgesics |
| Total                     | 0-24  | Ankle or knee                                                               |
|                           | 0-22  | Elbow                                                                       |

FROM, full range of motion; ROM, range of motion.
* Limping, walking with foot turned out, walking on side of foot, no push-off, walking on toes, uneven strides, no or uneven weight shifting, abnormal running, galloping, skipping or stairs.

skills. Activities suggested for strength testing are displayed in Table 8.3.

Gait

It is important to include gait in the evaluation of the knee and ankle because problems in joint function will be magnified through gait activities including walking, running, hopping, galloping and skipping. Ascending and descending stairs may also elucidate subtle joint abnormalities. A gait evaluation should include all of the above activities, taking into account the developmental age of a young child. A child younger than 5 years will not be able to skip. If the child is developmentally unable to perform a skill activity, then that activity should not be used to determine the gait. Functional components of the knee and ankle necessary for normal gait are shown in Table 8.2.

Pain

Pain is a subjective discomfort during rest or active use of a joint. Pain is best measured using a Likert scale that has been validated for age. Pain in children is assessed using the ‘Faces’ scale widely employed to assess child pain during hospitalization [35].

Current issues in physical joint examination scales

In order to develop a joint examination instrument that will fulfil the needs of haemophilia providers internationally for use both in clinical care as well as an outcome instrument for use in clinical trials, several tasks must be accomplished. The instrument must be validated both in healthy individuals as well as in persons with haemophilia. Each component of the scale must be subjected to scrutiny for validity and predictive value. Finally, the scale should be compared with a ‘gold standard’.

1 Validation of joint examination instruments. The WFH PE scale was never subjected to validation procedures that have subsequently become standard for development of outcome instruments. The CYC scale is currently being validated in 70 healthy boys without haemophilia between the ages of 1 and 7 years to establish normal values. The Colorado ‘Half-Point’ scale will be validated in healthy boys from 8 to 18 years. Inter-rater reliability will be determined for each of the scales. These scales will be applied to an ongoing prospective randomized clinical trial of routine (prophylactic) and episode-based (on-demand) factor concentrate replacement regimens to test the sensitivity and specificity of these scales to discriminate joints relative to number of haemorrhages or structural abnormality on objective imaging study.

2 Critical evaluation of the usefulness of each of the physical examination elements. Clinical experience predicts that joint angulation will not discriminate children with haemophilia from healthy children. In addition, crepitus may not be a very specific sign of haemophilic arthropathy. Young children may be unable to understand the concept of time, and questions regarding pain, other than in the immediate moment, may have little meaning. These clinical questions should be answered shortly by ongoing validation studies.

3 Comparison of the physical joint assessment with a ‘gold standard’. New instruments are generally validated in reference to an existing standard. A physical examination instrument can
be validated in reference to joint anatomy determined using an objective imaging technique such as MRI or to the number of haemorrhages suffered by that joint. Both of these referent standards have intrinsic limitations.

Use of physical and imaging assessment tools for persons with haemophilia has the same overall goal: that is, to determine evidence for acute and chronic musculoskeletal damage. However, these measurements are innately different and cannot be compared directly. Imaging tools, particularly sensitive tools such as MRI, can determine minimal evidence of changes in soft-tissues as well as abnormalities of cartilage and bone that may not be appreciated on physical examination or plain X-ray. Often, small children present with mild alterations of gait and pain, without obvious joint swelling or loss of range of motion. While MRI examination is rarely performed to diagnose an acute joint haemorrhage, in a young child with severe haemophilia the presence of increased joint fluid on MRI supports the diagnosis of intra-articular haemorrhage as opposed to soft-tissue bleeding around the joint. This information may be used to support the initiation of prophylaxis at the time of first questionable joint haemorrhage. Occasionally, mild joint swelling is determined in a child without a history of clinical joint haemorrhage. The presence of haemosiderin and early synovial hyperplasia on MRI confirms the clinical impression of joint haemorrhage and can be used to guide clinical treatment. MRI can be used to support suspicions raised on physical examination. In this case, imaging can confirm findings suggested on physical examination.

In some clinical settings, functional physical examination and bony structural evaluation can be discordant. A person with mild to moderate haemophilic arthropathy may, with the aggressive use of infusion and physical therapy, regain strength, range of motion and gait. Muscle bulk may be restored if full range of motion is achieved. It is especially important to restore maximal physical function in young children in whom future growth has the potential to magnify either healthy physical growth or atrophy. However, bone and cartilage lesions are not reversible in persons with haemophilia with either infusion or surgical therapies. Early in the course of structural damage the physical examination score may low, but the imaging score may be high. Persons with fully restored physical function but objective evidence of cysts or erosions on MRI will have slow progression of structural lesions over time, but may be fully functional and pain-free for a period of time. Discordance between functional and structural outcomes in such patients confirms both the failure of past infusion therapy to prevent the initial (and potentially progressive) structural lesions of haemophilic arthropathy and simultaneously supports the efficacy of subsequent infusion and exercise therapies to restore limb function. Unfortunately, progressive structural damage eventually causes chronic pain that results in physical signs and scores on imaging and physical examination evaluations tend to converge. It is necessary to establish the relationship between structural and functional assessments over time and to clearly define the use of comparative assessments.

Formation of an international committee for prophylaxis in haemophilia

Current questions regarding optimal physical joint examination and other related issues affect the global community of persons with haemophilia and require international collaboration for comprehensive answers. An international committee has been formed within the World Federation of Haemophilia and the International Society for Thrombosis and Haemostasis to examine, specifically, issues in prophylactic therapy for haemophilia. A working party of this committee has been formed to consider the issues raised here regarding physical joint examination and will develop assessment standards for the international community.

Conclusions

Joint physical examinations are the cornerstone of musculoskeletal evaluations for persons with haemophilia. Joint physical examination can be performed in a variety of settings, is inexpensive and independent of expensive technology. However, the value of joint physical examination is highly dependent upon the skill and experience of the examiner. In addition, the assessment tool for haemophilia must be appropriate for the developmental age of the patient and the expected degree of severity of physical abnormalities. Current and future efforts engaging the international community of haemophilia health-care providers is necessary to establish and validate useful scales for joint physical examination and to monitor and improve these scales continuously to meet current and future musculoskeletal assessment needs.

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References

Joint surgery in patients with inhibitors

S. Schulman for the rFVIIa-CI Group (see Appendix)

Introduction

The occurrence of an inhibitor is today the most feared complication in the treatment of patients with haemophilia, since the problem with transfusion-transmitted viral disease has become controlled through the introduction of efficient viral elimination steps in the manufacturing process of factor concentrates. In at least half of these patients the inhibitor is transient, sometimes hardly noticeable and easily overcome by continued infusions of factor concentrate. However, in 10–15% of patients with haemophilia A, 2–3% of patients with haemophilia B and a few per cent of patients with von Willebrand’s disease (VWD) type 3 (severe form) the inhibitor remains and constitutes a major obstacle for effective prophylaxis against joint haemorrhage and for prompt treatment when a bleeding occurs. These patients are not able to enjoy the benefits of prophylaxis with factor concentrates and will therefore develop the chronic arthropathy and muscular atrophy typically seen in persons with haemophilia lacking proper treatment.

Patients with haemophilia and inhibitors will thus be in need of orthopaedic surgery at a younger age and to a larger extent than most haemophiliacs without an inhibitor. Paradoxically, inhibitor patients will often be the ones denied surgery or having to wait the longest time for the operation. This is because of the difficulties that any surgical procedure entails in patients with an inhibitor for whom, until recently, effective haemostasis could not be granted. If at all, surgery was only chosen as a last resort for life-threatening conditions.

General principles

Elimination of the inhibitor

Immune tolerance therapy is a successful tool for elimination of the inhibitor and has a permanent effect in 63–83% of patients with haemophilia A but perhaps only in one-third of patients with haemophilia B [1]. It should therefore be attempted before surgery—if time allows for it. Predictors for a successful outcome of this therapy are historical peak inhibitor titre and the titre at the initiation of the immune tolerance therapy [1]. The former is hard to control whereas the latter is to some extent time-dependent. However, it is not always possible to wait for the titre to decrease to a low level, such as less than 10 Bethesda units (BU). In addition, the interval between the detection of an inhibitor and start of immune tolerance therapy was in one registry (International Immune Tolerance Registry) a predictor for the outcome [2,3]. It would accordingly be preferable to start this treatment as early as possible. Taking into account the high doses of factor concentrates used for this treatment, and that they are based on body weight, an early start in the young child will definitely be an economic advantage, in spite of the cost of a central venous access.

Transient elimination of an inhibitor immediately prior to surgery is another possibility. This can be achieved with plasmapheresis for very low-titre inhibitors, but for high titres extracorporeal protein A adsorption (haemophilia A with inhibitor) or immunoaffinity adsorption (haemophilia B with inhibitor) is required [4,5]. The patient will then respond to treatment with the missing coagulation factor, but after approximately 5 days the inhibitor titre rises sharply (anamnestic response) and is at that point usually impossible to overcome. For this reason it is common practice to combine the transient elimination with induction of immune tolerance, using very high doses of the coagulation factor (Bonn protocol) and also the combination of cyclophosphamide and intravenous gammaglobulin (Malmö protocol) [5], so that, in the long term, permanent elimination of the inhibitor can be accomplished.

Surgery with the inhibitor present

In adult patients with haemophilia and a long-standing high-titre inhibitor, elimination of the latter is usually not feasible. In these cases, haemostasis can be achieved by either bypassing the step in the coagulation system where the missing factor is needed or by avoiding the neutralizing effect of the inhibitor. The therapeutic options are activated coagulation factors and porcine factor VIII (FVIII), respectively.

The first attempt to bypass FVIII, in the case of an inhibitor, was with prothrombin complex concentrates (PCCs). An effect
that was more than that of placebo was demonstrated in a randomized study against albumin in patients with haemarthrosis [6]. This effect is usually considered too low or unreliable for major orthopaedic surgery. Activated prothrombin complex concentrates (aPCCs) are in turn slightly more effective than PCC. Two aPCCs, FEIBA (Immuno AG, Vienna, Austria; currently Baxter Bioscience, Vienna, Austria) and Autoplex (Baxter, Glendale, CA) have been compared with PCCs for mild to moderate bleeds in randomized trials [7,8], but the differences achieved were not statistically significant in either of the two trials performed. With an overall effectiveness of aPCCs of about 55–60% in these studies, this alternative was also not considered sufficiently safe for major elective orthopaedic surgery. Subsequently, a change of opinion has occurred, related to a more pragmatic choice of time point for evaluating the haemostatic effect. Instead of assessment at 6 h [8] or at 24 h [7], a more global measurement of effect after a few days was used in uncontrolled cohort studies of FEIBA®, reporting satisfactory haemostasis in 80–93% of the bleeding episodes [9,10]. At this level of efficacy many centres are prepared to perform major elective surgery.

A bothersome feature of aPCCs is that, because of its composition of several coagulation factors in unactivated as well as activated form, no reliable test for monitoring of its effect has been identified, and thus no therapeutic range is applicable. Repeated injections of high doses of aPCCs can generate excessive activation of systemic coagulation, which may lead to disseminated intravascular coagulation (DIC) [9,11] and/or myocardial infarction [12], even in young patients without pre-disposing pathology in the blood vessel walls. Nevertheless, in a review of all published and also unpublished thrombotic events in patients treated with FEIBA, 16 such events were documented, corresponding to an incidence of merely 4 per 105 infusions [13].

A more refined version of the ‘bypassing strategy’ is recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), which is the only activated coagulation factor that can be present in the blood circulation in significant amounts without causing harm. Only when bound to tissue factor, which is present at the site of injury, will the FVIIa–tissue factor complex initiate coagulation by activation of factor IX and factor X. There is also a tissue-factor-independent effect of rFVIIa, when given in high doses. Monitoring of the treatment can be carried out with ease, using one-stage clotting assay for FVII. The more expensive assay for FVIIa does not contribute additional information. However, a therapeutic range has not yet been established with certainty. Typically, FVII levels are kept above 10 IU/mL and anywhere up to about 50 IU/mL for surgery. Treatment with rFVIIa was assessed as excellent or effective in 79% of haemarthroses and 63% of muscle bleeds in a compassionate use programme [14].

A different strategy is to trick the inhibitor by using porcine FVIII, which has some different epitopes, especially at the sites of the FVIII molecule where neutralizing antibodies are often directed. Yet, the procoagulant effect of porcine FVIII in human blood coagulation is not inferior to the human variant of FVIII. In cases of a low antibody cross-reactivity against porcine FVIII, this factor concentrate is an appealing alternative, which can be monitored using a routine FVIII assay, and the therapeutic range similar to human FVIII. With high antiporcine inhibitor titres the haemostatic effect is drastically diminished but, overall, porcine FVIII (Hyate-C, Speywood Pharmaceuticals Ltd, Wrexham, UK; currently Beaufour Ipsen, Berks, UK) was reported to provide a fair to excellent response in over 90% of 491 haemorrhagic episodes in hospitalized patients worldwide [15]. The availability of porcine FVIII concentrate has lately been very limited because of problems with porcine parvovirus and restrictions of import from the UK related to foot and mouth disease.

Finally, it should not be forgotten that in patients with a low-titre inhibitor, and preferably with a strong anamnestic response in the past, treatment with a regular human FVIII concentrate in higher doses than normally used can be very effective if the inhibitor is neutralized. Whether this is achieved more effectively with injections of large bolus doses or with continuous infusion of FVIII is an unresolved issue.

Planning of the procedure

Major surgery in a person with haemophilia, complicated by an inhibitor, requires the best and most experienced expertise available. This applies to the haematologist as well as the surgeon, but also to the physiotherapist. The haematologist should have experience from treating haemophiliacs with different titres of inhibitors using more than one of the factor concentrates mentioned above. The haematologist has to be present during the entire surgery, and preferably stay in the operating room during the procedure. Immediate action in the case of complicating haemorrhage is crucial. Postoperatively, the haematologist and nurses from the coagulation service should visit the patient a few times daily.

The orthopaedic surgeon should be informed about the special and demanding scenario and be prepared to spend ample time ensuring optimal surgical haemostasis. Oozing from bones can be sealed with wax. A discussion in advance of all the steps during the procedure is recommended, and the least traumatic alternative should be chosen, for example radioactive synoviorthesis rather than surgical synovectomy. The use of fibrin glue should also be considered, although some surgeons do not find it beneficial.

The physiotherapist needs to know what the presence of an inhibitor entails and that too brisk mobilization of the joint and of the patient may result in a devastating haemorrhage. The nurses on the surgical ward also need to be taught about haemophilia, inhibitors and what they should watch out for. It is also helpful to engage family members and, last but not least, the patient himself in the plans and procedures, so that he can remind the nurses if a dose of factor concentrate appears to be
delayed or missed or watch the infusion device now and then and understand the alarm functions.

Preoperative tests

In addition to the routine tests for blood count, electrolytes, renal function, blood group and cross-match, some specific analyses may have to be performed in haemophilic patients. An inhibitor titre should be obtained shortly before the day of surgery in all patients except those with a long-standing high-titre inhibitor, where no change is to be expected. A low titre may have decreased to zero, which will allow for initial treatment with the missing factor. Conversely, it may have risen to a much higher level as a result of a recent treatment episode, when the patient became exposed to the missing coagulation factor and had an anamnestic response.

If it is planned to use rFVIIa, especially in continuous infusion, a single-dose pharmacokinetic evaluation is strongly recommended, because of the wide variation in clearance of rFVIIa [16]. It is easily carried out with one injection of rFVIIa at a dose of 90 mg/kg and blood samples for FVII before, 10 and 30 min, 1, 2, 4 and, if possible, 6–8 h after the injection. The clearance is then computed; the maintenance infusion rate will equal the product of the clearance (in mL/h/kg) and the desired steady state concentration (in IU/mL). The specific activity of rFVIIa is about 50 000 IU/mg. In case of emergency surgery, we have still managed to perform such an evaluation with limited blood sampling. The preoperative bolus dose was then also the pharmacokinetic ‘single-dose’. Blood samples were obtained before, and then intraoperatively at 10, 30, 60 and 120 min after the injection, the last one immediately followed by a new bolus dose and then a continuous infusion, based on preliminary FVII one-stage clotting assay results from our coagulation laboratory.

On the other hand, if the inhibitor titre has decreased from a low titre to zero in the absence of exposure to the coagulation factor, a pharmacokinetic evaluation with that factor should not be performed during the days before surgery, in order to maximize the time from surgery until the anamnestic response occurs. Instead, a factor level should be obtained 30 min after the preoperative bolus dose and analysed immediately, so that recovery can be calculated by the time the patient leaves the operating room. That will give a rough estimate of the factor requirements that can be expected during the first postoperative days.

Clinical experiences

aPCCs

In some countries aPCCs, mainly FEIBA, is still considered the drug of choice for surgery in inhibitor patients, as in the recently reported Norwegian experience with eight minor and four major surgical procedures, one of which was orthopaedic—a total knee replacement [17]. However, there were haemorrhagic complications in two of the major surgeries, including a drop of haemoglobin to 40 g/L after a knee arthroplasty, and a subendocardial non-fatal myocardial infarction after another of the major procedures. In a recent compilation of orthopaedic operations in patients with inhibitors, Hvid and Rodriguez-Merchan [18] had identified nine cases treated with PCCs or aPCCs. These included synovectomies (four), total hip and total knee arthroplasty (one each), arthroscopy (one), removal of pelvic pseudotumour (one) and fasciotomy with skin graft (one).

Porcine FVIII

In the same review [8], cases treated with porcine FVIII in connection with major orthopaedic surgery were found, including total knee and total hip arthroplasty (three and one, respectively), osteotomy-osteosynthesis, synovectomy, elbow disarticulation and resection of pseudotumour (one each), with good results except in two, where it was ‘fair’ [18]. Adverse events with porcine FVIII have, in general, been few since the purification technique was improved, amounting to 2.3% in hospitalized patients and 0.64% in home treated patients [19].

rFVIIa

The very first treatment with this concentrate was for surgical synovectomy of the left knee in my own patient [20]. We were questioned afterwards as to how we could use a completely new drug as the only haemostatic agent for such a major and quite traumatic procedure. Part of the answer was the convincing preclinical data, together with positive experiences from plasma-derived FVII in minor surgery. However, the circumstances for the patient involved also contributed to this choice. He had a high-titre inhibitor, had failed to respond to induction of immune tolerance, had a very variable response to aPCCs and no response to porcine FVIII, and most of all, he was desperately asking for effective relief from his recurrent haemarthroses and pain. A few years later he underwent simultaneous synovectomy of the right knee joint and the left ankle [21]. In both surgeries rFVIIa was given with bolus doses, 54 mg/kg in the former and 95 mg/kg in the latter. The lower dose was effective, because of a favourably low clearance in this patient, but for the second procedure we chose to follow the generally recommended dosage.

Doses ranging between 89 and 118 mg/kg of rFVIIa have also been used for 12 major procedures in the compassionate use programme [22], and these included synovectomy of the knee joint (two), single and bilateral total knee arthroplasty (two and one, respectively), amputation of lower limb (one) and removal of pseudotumour (one). The total dosage of rFVIIa for these operations was 495–1306 mg. There was no uncontrollable bleeding or change to other haemostatic agents.
Dose of rFVIIa

The size of the dose of rFVIIa has been subjected to a randomized clinical trial, where 35 and 90 mg/kg were compared [23]. The series included 11 major procedures, out of which 10 were orthopaedic: synovectomies (five), total hip replacement (two), knee joint manipulation, cartilage repair of the knee and bone graft (one each). The 35 mg/kg-dose appeared insufficient for at least major surgery, because as many as three patients with synovectomy had inadequate haemostasis requiring additional bolus doses of rFVIIa, switch to porcine FVIII or to human recombinant FVIII, respectively; one patient needed transfusions during and after total hip replacement and additional doses of rFVIIa. In the high-dose group, one patient with cartilage repair was switched to FEIBA.

Mode of administration of rFVIIa

Until 1995, rFVIIa was only administered as bolus injections because the limited data available on the stability of the product after reconstitution suggested that activity was rapidly lost. This was true for dilution in Ringer lactate but with reconstitution in the diluent provided by the manufacturer and without any further dilution, the stability is excellent over at least 1 week at room temperature [24]. Administration by bolus doses requires timely injections every 2 h during the first 1–2 days after surgery, thereafter with increasing intervals, based on the half-life of approximately 2.7 h [25]. There is a risk that an injection is missed, which may result in postoperative bleeding, and the routine is inconvenient. For that reason, continuous infusion of rFVIIa has been attempted [24] and by now a large number of treatments for haemorrhage or surgery have been compiled with a previous update in 2000 [16]. However, this mode of administration has come under debate, and the results have varied considerably between centres. This was demonstrated in the October 2001 issue of *Thrombosis and Haemostasis*, where two cohort studies on continuous infusion with rFVIIa for surgery were published, but with diverging results. The British multicentre study included eight patients, with orthopaedic surgery in six (total knee and total hip arthroplasty in three each), who received a fixed infusion rate of rFVIIa at 16.5 mg/kg/h [26]. Five of the eight patients (four of six with arthroplasty) suffered bleeding complications. In the Italian multicentre study, 25 surgical procedures were performed, all of which were major, including seven orthopaedic cases (total knee arthroplasty in six and femoral osteosynthesis in one), covered with rFVIIa at a median infusion rate of 20 mg/kg/h [27]. In one of the orthopaedic cases severe bleeding started 1 day after the arthroplasty, and on day 3 the patient was switched to bolus dosing and tranexamic acid.

These studies require some comments. In the British study, tranexamic acid was not used at all and in the Italian study when the physician in charge decided its use. Data from the registry on continuous infusion with rFVIIa has shown a significantly lower incidence of bleeding complications when tranexamic acid was used concomitantly [28,29]. In the British study, there were several confounding problems. Two patients did not receive the study drug as intended as a result of infusion pump failure or extravasation, one had surgical bleeding and one had a wound infection. Two patients with complications had levels of FVII 6 IU/mL on day 3, which was probably inadequate for haemostasis and, with the substantial range of clearance of rFVIIa also seen in this study (18–100 mL/h/kg), it is understandable that some patients will have too low a FVII level from a fixed dose of 16 mg/kg/h. Preoperative pharmacokinetic evaluations and individually calculated maintenance dosing is therefore recommended.

Continuous infusion of rFVIIa has also been blamed for causing DIC [18]. The case referred to was our own, which has been described previously [29]. Briefly, the patient had a massive pseudotumour occupying the left half of the abdomen and pelvis, penetrating via the ilial bone and expanding actively to the flank region and down the thigh. The pseudotumour was infected by *Clostridium perfringens* and filled with gas bubbles, only partly controlled with antibiotics. Excision of the pseudotumour was performed on vital indication, but surgical haemostasis was impossible to achieve at the fresh expansion sites. Hypovolaemic and septic shock developed, with ensuing DIC. Under these circumstances, it is hard to believe that the DIC was caused by continuous infusion.

A new study with continuous infusion of rFVIIa for surgery is currently being conducted, using a fixed dose of 50 mg/kg/h with a target FVII level of 30 IU/mL. So far nine patients, all with major orthopaedic surgery, have been treated without excessive bleeding from the surgical wound but with bleeding adverse event (at other sites) in several of the cases, necessitating additional bolus doses (MP Smith, Meet-the-expert session, XXVth WFH World Congress, Seville, May 2002). With this dose there is no economical benefit compared to bolus dosing, only an advantage regarding convenience.

Registry for continuous infusion with rFVIIa

Beginning in 1997, a questionnaire on continuous infusion has been mailed on several occasions to haemophilia centres known to have used rFVIIa. Responses have been collected from 34 centres worldwide. The cases from the above mentioned Italian study are included here. In total, data on 67 surgical procedures have been registered, of which 35 were orthopaedic; some details are listed in Table 9.1. There were 10 minor or major bleeding complications, but in four cases low-molecular-weight heparin had been given. At least three of the patients with bleeding had not received treatment with a fibrinolytic inhibitor. One patient with total knee arthroplasty had received rFVIIa in bolus doses for the first 3 days and bled initially, but there were no complications after he had been switched to continuous infusion [30].
Table 9.1 Characteristics of orthopaedic surgery performed with rFVIIa in continuous infusion. Updated Registry of the rFVIIa-CI Group. Coagulopathy is haemophilia A with inhibitor, unless otherwise stated.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of cases</th>
<th>Days on continuous infusion median (range)</th>
<th>No. with bleeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total knee replacement</td>
<td>13</td>
<td>11 (3-14)</td>
<td>4</td>
<td>Cellulitis with some oozing; paravenous infusion; 2 days after end of infusion; one ineffective ≥ bolus doses. ½ had received low-molecular-weight heparin subcutaneously 1 day after end of infusion; ¼ received low-molecular-weight heparin</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>7</td>
<td>14 (13-28)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Knee arthrodesis</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ankle arthrodesis</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>Excision of ankle osteophytes</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>Removal of infected hip prosthesis</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>Patient was septic</td>
</tr>
<tr>
<td>Removal of osteosynthetic material</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>Bled from end of surgery, DIC?</td>
</tr>
<tr>
<td>Manipulation of knee contracture</td>
<td>2</td>
<td>3.5 (3-4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Excision of infected pseudotumour</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>DIC (see text)</td>
</tr>
<tr>
<td>Chemical synovectomy</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthroscopic meniscectomy</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>Open evacuation of knee</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hand surgery</td>
<td>2</td>
<td>6.5 (5-8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Laminectomy</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>Factor XI deficiency</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation; FVII, factor VII.

Caveats for continuous infusion of rFVIIa

Continuous infusion of rFVIIa is not included in the labelling of the drug, and therefore this mode of administration cannot be recommended by the manufacturer. Any physician who decides to use this mode should be familiar with all of the pitfalls and realize that if complications occur, there is a greater risk of liability than with bolus injections. Surgery in infected areas will always create a high risk of complications. The minipump for continuous infusion must be reliable with multiple alarm functions and also regularly monitored by staff. Our experiences with the CADD-pump (Pharmacia Deltec, St Paul, MN, USA) are excellent [31]. A parallel infusion with saline at 20 mL/h in the same peripheral vein catheter will reduce the risk of thrombophlebitis. Tranexamic acid should be used concomitantly, except when there is an absolute contraindication, e.g. macroscopic haematuria. Treatment should under any circumstances start with at least one bolus dose of 90 mg/kg intravenously. In the case of very traumatic surgery, including total hip arthroplasty, at least 2–3 bolus doses every 2 h should be given before initiation of the continuous infusion. The maintenance level of FVII should be above 10 IU/mL, except for total hip arthroplasty and similar procedures, where it should be at least 20 IU/mL for the first 2–3 days. Because the FVII level is not very predictive of outcome, it may be advisable to use an additional test. Ideally, this should be a global analysis of haemostasis, but so far this has not been evaluated in clinical situations. A substantial shortening of the prothrombin time may add some useful information.

Independent of the mode of administration of rFVIIa, there is a certain risk—albeit small—of thrombotic complications [32]. It may be greater in patients with acquired haemophilia than in congenital haemophilia with an inhibitor. Under any circumstances, the risk of bleeding is definitely greater than that of thrombosis, and therefore systemic thromboprophylaxis with unfractionated or low-molecular-weight heparin is not justified in inhibitor patients.

Planned switch of therapy

There is some experience of planned switching of factor concentrates postoperatively. In a small series of six operations in four patients with haemophilia A and inhibitors, treatment started with FVIII [4]. In some cases the inhibitor titre had been brought down preoperatively with immunoadsorbent therapy.
On day 4–6 postoperatively there was always an anamnestic response, and treatment was changed to rFVIIa. No complications occurred. We have performed orthopaedic surgery on four occasions (uni- and bilateral total knee arthroplasty in two and one, respectively, and ankle arthrodesis in one) in three patients with low-titre inhibitors, two with VWD type 3 and one with haemophilia A. At the time of surgery the titre was zero, but on day 4–5 there was always an anamnestic response, which was impossible to overcome even with high doses of the factor concentrate. The patients with VWD were then switched to FEIBA and the one with haemophilia to rFVIIa, because many years ago he had a minor myocardial infarction after treatment with PCC.

Conclusions

Until a decade ago, major surgery in patients with haemophilia and an inhibitor was extremely rare. However, since then substantial experience has been accumulated regarding adequate haemostatic treatment to cover these patients during any kind of surgery. There are more data on treatment with rFVIIa, in different doses and different modes of administration, than on aPCC. Thrombotic complications are rare, but have been described with both drugs; bleeding complications are more common. In addition to the drug therapy, the preparations for surgery as well as the surveillance during and after the procedure are crucial for a successful outcome in these complicated scenarios.

Joint surgery requires effective haemostasis in order to reduce wound haematoma, which may ultimately become infected and jeopardize the long-term outcome. The situation in persons with haemophilia and an inhibitor brings matters to a head and different treatment options for these patients have been discussed. Side-effects associated with the different therapeutic agents are important to consider. Studies on rFVIIa have yielded good results for arthroplastic surgery. An update on the worldwide experiences of rFVIIa in continuous infusion has also been presented.

Appendix

The members of the rFVIIa-CI Group are:


References


Chronic haemophilic synovitis
Multilevel surgery in a single operative session for persons with haemophilia: considerations in patients with multiple deformities

A. Llinas and L. Heijnen

Introduction

The musculoskeletal care of persons with haemophilia often presents an unusual combination of elements: multiple deformities, high degree of technical surgical difficulties, elevated costs and elevated morbidity. The contemporary trend in polytrauma and cerebral palsy, where similar conditions exist, suggests that one may solve multiple lesions in a single event with multilevel surgery. However, there is a fine line that divides an aggressive surgical multilevel approach during a single procedure that will produce outstanding recovery in the patient, from one that will produce severe morbidity and result in a permanent loss of function. It is the role of the haemophilia care group to establish where the fine balance between risk and benefit lies, taking into account their collective expertise, resources and health-care setting.

We have defined a patient with multiple deformities as one who has structured articular or osseous deformities in one or more extremities to a level where they interfere with activities of daily living. In these patients, the coexistence of deformities yields a functional impairment that exceeds the sum of limitations that the individual restrictions caused by each lesion would produce otherwise. When the patient has lesions in a single extremity, in order to qualify in the category of patients with multiple deformities, he or she should have a minimum of two joints involved with a structured deformity, or one joint and one osseous deformity.

Treatment considerations of the haemophiliac with multiple deformities go beyond the technical aspects of rehabilitation and musculoskeletal surgery, because the elements that led to severe deterioration of the musculoskeletal function should be addressed. A profound analysis of the element, or combination of elements, that resulted in severe deterioration of the condition of the patient is indispensable in order to carry the treatment to completion successfully. Otherwise, the same elements that produced the deterioration of the musculoskeletal function in the first place will impede the restoration of function and productivity in the individual, and perhaps lead to recurrence.

An analysis of the patient's determinants of access to health care, socioeconomic conditions, nature of the haemophilia and the mix of articular and osseous deformities will yield a large number of combinations of characteristics. For this reason, an individual treatment plan should be tailored for each patient.

Definition of objectives

The expectation of a return to normal function of all four extremities following medical intervention, despite having being exposed to lengthy periods of musculoskeletal suffering and deterioration, is understandable. However, delivering this prospect may not be possible, so the patient, his immediate relatives and the haemophilia care group should discuss realistic objectives and agree upon those of mutual interest. Returning the patient to the best musculoskeletal condition possible with the least amount of suffering, delay and expense is undoubtedly the underlying aim; however, the definition of objectives should be precise and explicit.

Rehabilitation: diagnosis and planning

In order to determine the clinical sequence that the patient will follow, he will require a thorough evaluation from the point of view of rehabilitation and orthopaedic surgery in order to establish a precise diagnosis. In haemophilia, with greater emphasis than when treating other musculoskeletal conditions, no resources should be spared to restore function by non-surgical means.

The main aims of treatment are to relieve pain, increase range of motion and muscle strength, improve posture and maximize function. The modalities of treatment include manual therapy, including mobilization of joints and correction of muscle imbalances, hydrotherapy, electrotherapy including transcutaneous nerve stimulation (TNS), braces and splints, advice and
education. Additionally, serial casting, reversed dynamic slings and extension–desubluxation devices as well as intermittent compression systems may be useful in the management of flexion contractures [11].

From the point of view of rehabilitation, the diagnosis includes three levels: organ level, personal level and social level. This perspective was introduced by the World Health Organization's International Classification of Impairments, Disabilities and Handicaps (ICIDH, ICIDH-2) [2,3] and complemented by Post et al. [4]. At the organ level, the ICIDH refers to ‘impairment’, defined as any loss or abnormality of psychological or anatomical structure or function. At the personal level, the ICIDH refers to ‘disability’, as any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being. At the social level, the ICIDH refers to ‘handicap’, defined as a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfiment of a role that is considered normal for that individual. This diagnostic approach includes all measures aimed at reducing the impact of disabling and handicapping conditions and enabling the disabled and handicapped person with haemophilia to achieve social integration [5].

Only after a thorough effort has been made to achieve the maximum level of recovery of function should surgical treatment be considered [6–10]. It should be clear to the patient that the first level of the therapeutic armamentarium has been employed, and that moving up in the ladder of therapeutic options will bring about greater risk and potential morbidity.

**Orthopaedic surgery**

The difficulties in addressing multiple joint procedures during a single operation in a patient with haemophilia were outlined by Rothwell and Faed in 1979 [11]. They performed arthrodeses of the left knee and right ankle and total replacement of the left ankle for the treatment of a patient with severe haemophilic arthropathy. In 1996, Horoszowski et al. [12] published their experience with multilevel surgery during a single operative procedure in 11 haemophiliacs. This approach produced restoration of function, shortened rehabilitation period and yielded adequate control of pain and bleeding. The authors highlight the relevance of the availability of various technical resources to enhance homeostasis and minimize postoperative blood loss. For example, the use of aminocaproic acid, coagulation of extensive areas that oozed with CO₂ laser and the spread of fibrin glue to control bleeding [12,13].

The therapeutic protocol of Horoszowski et al. was able to yield a functional limb with a low complication rate and a shortened rehabilitation period, at the Israel National Haemophilia Centre; however, these results may not be reproducible in a less experienced haemophilia care centre in a developing country. Therefore, if the infrastructure is not sufficient to guarantee similar results to the ones described above, it may be safer to stagger the surgical procedures. This approach may increase the operating room costs as well as those from factor concentrates, but may minimize patient morbidity. As the haemophilia care team develops skill and practice, the group may move on to more ambitious single operative sessions where multiple surgical procedures are performed.

Balancing the cost : benefit ratio such that the patient will have maximum probability of success with minimal morbidity requires excellent judgement and the wisdom of the haemophilia treatment team. We have learned from the experience of Rothwell and Faed [11] and Horoshowski et al. [12] that the approach of multilevel surgery in a single operation is viable.

**Postoperative rehabilitation**

Multilevel surgery during a single operative procedure requires a comprehensive rehabilitation plan. The patient should consult with the rehabilitation team prior to surgery, in order to become familiar with the routines he will experience after surgery. Developing a rapport with the team prior to surgery has proven helpful in our experience. Third-party payers should be made aware of the relevance of performing rehabilitation within the institution where the haemophilia team operates, and of the high value of physical therapy as a determinant of success of the surgical procedure.

In developing countries, with little or no clotting factor available, rehabilitation should not only include physiotherapy, prescription of orthoses, walking aids and other adaptations, but also the education of haemophilic patients and their families.

The high cost of factor concentrates is typically at centre stage of any discussion in a developing country, overshadowing other complex problems that are prevalent. One of these problems is the difficulty in providing adequate rehabilitation for haemophiliacs on an outpatient basis. The nature of the problems span from the basic logistics of transportation to and from the rehabilitation clinic, to the complexities of access to integral health-care coverage. Rehabilitation of a haemophiliac after a single joint reconstructive procedure with an appropriate supply of concentrate is a challenging proposition. Attempting the same, but after multiple simultaneous orthopaedic reconstructive procedures and on a lean supply of concentrate, is a challenge to ingenuity.

The World Health Organization have developed a manual for the successful execution of community-based rehabilitation (CBR) [14]. The aim of the programme is to provide rehabilitation within the community, using resources that are available locally, to avoid the complexities of travelling to a remote health-care centre, and improving compliance [15]. The manual for the establishment of a CBR contains 34 modules and is designed to be developed by local supervisors, community workers and persons with disabilities.
Conclusions

Multilevel surgery during a single operation is a viable strategy. The extent to which it should be implemented must vary according to the collective expertise of the haemophilia care group, resources and health-care setting. A multidisciplinary approach is required to decipher the complexities that led to the deterioration of the musculoskeletal function in order to produce a functional individual, with the ultimate goal of achieving social integration.

References


Radioactive isotopes for radiosynoviorthesis

J. Coya-Viña, M. Marin-Ferrer and L.M. Martin-Curto

Introduction

A radioactive isotope, also referred to as a radioisotope, is defined as a substance emitting radiation. It consists of an unstable nucleus, in which the ratio of neutrons to protons is not equal to 1; in other words, it is a neutron-excess nucleide [1, 2]. From the isotope disintegration process, three different types of radiation are emitted: alpha (α), beta (β) and gamma (γ) radiation [3]. Only beta and gamma radiation are of clinical concern.

Key concepts

Table 11.1 outlines the main features of the different radiation emitted by radioisotopes of use in nuclear medicine. Beta radiation consists of high-speed small-mass particles, whose speed is similar to that of light. It presents varying energy, with ionizing characteristics. Although its penetration power is not high, it can be locally absorbed. Because of its ability to ionize and interact with matter, it has high local irradiation power. These features render beta radiation useful for therapy in a series of clinical settings.

Gamma radiation is a form of electromagnetic radiation. X-rays and gamma rays are, among others, types of gamma radiation. Gamma radiation energy is steady in nature, but its energy is less than that of beta radiation particles. Unlike the latter, its penetration power is high. Hence its usefulness for functional imaging for diagnosis in a series of nuclear medicine procedures, especially in radioisotope scanning. Some radioisotopes (e.g. 198Au) emit both beta and gamma radiation. Others, such as 90Y, emit pure beta radiation particles. Some radioisotopes, such as 99mTc, emit only gamma radiation.

When using radioactive isotopes for clinical purposes, it is important to take into account its radioactive half-life, defined as the time taken for the disintegration of the half atoms of a radioactive material, which should not be mistaken for mean life. A distinction between radioisotopes and radiopharmaceuticals should be made. A radiopharmaceutical is a drug of clinical significance containing an isotope as an essential component and, at the same time, other substances which do not exert any pharmacological effects on the organism (i.e. the isotope carrier). Therefore, the term radioisotope should not be used as synonymous for radiopharmaceutical because it may be misleading. For example, colloidal 198Au is a radiopharmaceutical.

The current measurement unit for radioisotopes is the becquerel (Bq), and the megabecquerel (MBq). Nowadays, however, it not uncommon to encounter the former measurement unit, the milliCurie (mCi) in many papers and textbooks. The formula for the conversion of mCi into MBq is the following: 1 mCi = 37 MBq, and 1 mCi = 3.7 x 10^10 disintegrations per second.

Radiosynoviorthesis (radiation synovectomy) is an alternative procedure for surgical synovectomy in some cases of arthritis. The term radiosynoviorthesis refers to treatment of arthritis by means of radioactive isotopes. In this procedure, radioisotopes emitting beta radiation are used selectively to radiate the synovial
membrane, sparing articular cartilage tissue [4]. In this way, a significant improvement of articular inflammatory symptoms is achieved. Work on rheumatoid arthritis treated by radioactive isotopes was first reported in 1952 [5]. Initially, colloidal gold (colloidal $^{198}$Au) was used [6]. With the advent of other isotopes, such as $^{90}$Y [7–9], $^{186}$Re [10] and $^{169}$Er [11–14] which provide better clinical outcome, colloidal $^{198}$Au fell out of favour.

Properties of isotopes used for radiosynoviorthesis

Isotopes used for arthritis treatment are to meet a set of physical, chemical and biochemical properties [15]. First, the candidate isotope is to be a beta-particle emitter radioisotope, capable of being absorbed by the synovial tissue for a certain time required to accomplish the therapeutic effect with sparing of bone marrow, articular cartilage and other neighbouring soft tissues [4,16].

The radioactive isotope to be used is irreversibly bound to a particle, most often a colloid. A radioactive isotope irreversibly bound to a particle is referred to as a radiopharmaceutical. Particles should be of approximately 2–5 μm in size [17], so that they can undergo phagocytosis by the synovial membrane. However, too small a size may prevent phagocytosis by the membrane because the particles leave the joint too soon. Therefore, therapeutic effect is mainly dependent on physical, chemical and biochemical properties of the radioactive isotope, including its radioactive half-life, and on the delivered dose.

Pharmacodynamics

The pharmacodynamics of radioactive isotopes used for radiosynoviorthesis is not fully understood. However, there is evidence from experimental animal models and arthroscopy performed following isotope synovectomy that, once intra-articularly injected, the radiopharmaceutical selectively delivers radiation to the synovial membrane and, to a lesser extent, to the articular cartilage tissue by a direct action of emitted beta radiation. This leads to synovial membrane thickening and increased cell infiltrate and fibrin deposition on the superficial synovial membrane layers [18,19]. In addition, there is evidence of superficial synovial membrane layer capillary occlusion.

Within a few weeks to months, a significant amount of interstitial fibrous tissue is seen, which may affect the vessels, with interspersed areas of normal synovial tissue, [20]. Furthermore, reduced superficial synovial layer vasculature can be observed. Also, in this later stage, decreased synovial membrane thickness may be noted. A year after isotope synovectomy, vessel occlusion and perivascular fibrosis of synovial membrane can be seen.

In summary, the beneficial effects of beta radiation from radioactive isotopes used for radiosynoviorthesis consist of decreased oedema and deposition of synovial fluid, both contributing to arthritis pathogenesis. Decreased oedema and synovial fluid deposition results, in part, from interference of beta radiation with inflammatory events occurring in endothelial cells. On the other hand, vascular occlusion and fibrosis contribute to pain clearance in most cases [21].

Radiopharmaceuticals used for radiosynoviorthesis

It is important to select both the radiopharmaceutical and the dose for radiosynoviorthesis. Taking into account beta radiation penetration power, a basic rule for radiopharmaceutical selection is that the smaller the joint to be treated, the lower should be the radiopharmaceutical penetration power; in other words, radiopharmaceutical choice should be made based on the characteristics of the joint to be treated.

As far as the dose to be administered is concerned, it should be borne in mind that a precise accurate estimation for each case is unfeasible. According to our own clinical experience and recommendations by other authors [22], dose selection should be based on the following factors: size of the joint to be treated, size of the articular space, synovial membrane thickness and structure, and inflammation severity caused by synovitis.

The following discussion will focus on three of the radiopharmaceuticals most frequently used for synoviorthesis [16,21,22] (Table 11.2). They are an integral part of our current clinical practice with excellent outcomes. In addition, a large body of literature is now available on these radiopharmaceuticals [13,16,21–28] (Tables 11.3 and 11.4).

### Table 11.2 Features of the radioisotopes most frequently used for radiosynoviorthesis.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$^{32}$p</th>
<th>$^{198}$Au</th>
<th>$^{153}$Sm</th>
<th>$^{90}$Y</th>
<th>$^{186}$Re</th>
<th>$^{169}$Er</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioactive half-life (days)</td>
<td>14.3</td>
<td>2.7</td>
<td>1.9</td>
<td>2.8</td>
<td>3.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Radiation</td>
<td>β and γ</td>
<td>β and γ</td>
<td>β</td>
<td>β</td>
<td>β</td>
<td>β</td>
</tr>
<tr>
<td>Maximal penetration power (mm)</td>
<td>7.9</td>
<td>10.8</td>
<td>3.1</td>
<td>3.9</td>
<td>10.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Therapeutic penetration power (mm)</td>
<td>2.2</td>
<td>2.8</td>
<td>0.7</td>
<td>0.9</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>
THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES

Table 11.3. Clinical indications of the radioactive isotopes most frequently used for radiosynoviorthesis.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>90Y</td>
<td>Large-sized joints: knees</td>
</tr>
<tr>
<td>186Re</td>
<td>Middle-sized joints: shoulder, hip, elbow, wrist, ankle and tarsus</td>
</tr>
<tr>
<td>169Er</td>
<td>Small-sized joints: interdigitals</td>
</tr>
</tbody>
</table>

Table 11.4. Recommended isotopes and doses (MBq) for radiosynoviorthesis in different joints.

<table>
<thead>
<tr>
<th>Joint</th>
<th>90Y</th>
<th>186Re</th>
<th>169Er</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>185</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shoulder</td>
<td>-</td>
<td>74-111</td>
<td>-</td>
</tr>
<tr>
<td>Elbow</td>
<td>-</td>
<td>56-74</td>
<td>-</td>
</tr>
<tr>
<td>Wrist</td>
<td>-</td>
<td>56-74</td>
<td>-</td>
</tr>
<tr>
<td>Hip</td>
<td>-</td>
<td>185</td>
<td>-</td>
</tr>
<tr>
<td>Elbow</td>
<td>-</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Interdigital</td>
<td>-</td>
<td>-</td>
<td>18-37</td>
</tr>
</tbody>
</table>

MBq, megabecquerels.

90Y (yttrium)

Following radioactive gold (198Au) [29,30], yttrium is the most time-honoured radioactive isotope for arthritis treatment [28]. Although studies have failed to demonstrate any differences in clinical outcomes with colloidal 198Au and 90Y [30], colloidal gold has the disadvantage that it is not a pure beta radiation emitter and, in addition, once intra-articularly injected, may pass through lymphatics to internal organs, such as the liver. At the adequate dose, 90Y is reserved exclusively for large joints, particularly the knee. It is a beta radiation emitter isotope with a radioactive half-life of 2.8 days [31]. It is available in colloidal form with a maximal penetration power of 10.8 mm, its therapeutic penetration being equal to 3.6 mm. By therapeutic penetration is meant the thickness of soft tissue on which 90% of the absorbed dose is deposited [32]. The adequate dose is that best established by most authors [22,27,32-34], this being usually of the order of 185 MBq. A 56–100% reduction in symptomatology has been consistently reported [32,34–36].

186Re (rhenium)

Radiosynoviorthesis with rhenium (186Re) has been the focus of an important body of literature [22,24,37–39]. It is a beta radiation emitter isotope, with a small amount of gamma radiation. Its radioactive half-life is 3.8 days [21]. Maximal penetration power and therapeutic penetration are 4.5 and 1 mm, respectively [31]. As its penetration power is lower than that of yttrium, rhenium is reserved for middle-sized joints, such as wrist, elbow, shoulder, hip and ankle [22,24]. Like yttrium, rhenium is available in colloidal form (colloidal sulphur). In our current clinical practice, we deliver a dose of between 74 and 185 MBq (usually 111 MBq) for shoulder and hip, and between 56 and 74 MBq for wrist, elbow and ankle, 74 MBq being the most frequent dose [21,22,24]. Within this range of doses, improvement in symptomatology is achieved in 50–83% of cases [37,38].

169Er (erbium)

Erbium (169Er) is a radioisotope generally delivered in the form of colloidal citrate. Like yttrium, it is a pure beta radiation emitter. Its ability to penetrate into soft tissue is very low (1 mm), with a therapeutic penetration of only 0.3 mm [16]. Its radioactive half-life is 9.4 days [21]. Because of its low penetration power, it is indicated for isotope synovectomy of very small joints, such as interdigital joints [13,14,22,25]. We usually inject a dose between 18 and 56 MBq, most often 37 MBq. The dose is calculated largely empirically based on symptomatology, notably inflammation, of the joint to be treated. Clinical outcomes are quite promising, with symptomatology reduction in 76–79% of cases [23,36].

Imaging acquisition

In our opinion, it is important to obtain images to check adequate intra-articular isotope distribution. It is very important to predict therapy efficacy. As beta radiation emitter isotopes are injected for radiosynoviorthesis, they are not suitable for scintigraphical scanning, therefore we add to yttrium, rhenium or erbium a small dose (18 MBq) of a technetiated radiopharmaceutical (colloid-99mTc). Thus, we obtained a pure gamma radiation emitter substance that, once injected, does not interfere with radiosynoviorthetic therapy or have side-effects. An hour after injection of the radiopharmaceutical plus colloid-99mTc mixture, we conduct scintigraphical scanning of the treated joint (Fig. 11.1).

Complications

Radioactive isotopes should always be handled by a specialist, preferably by a nuclear medicine physician. From a legal point of view, Spanish legislation provides that physicians specialized in nuclear medicine handling radioactive isotopes must be licensed by the supervisor of radioactive facilities. As with other nuclear medicine procedures, radiosynoviorthesis requires patients’ informed consent [40], which we always ask for in both verbal and written form. When the treatment is adequately conducted by a specialist, to our knowledge, radiosynoviorthesis has no intrinsic side-effects. The only complications seen are related to puncture (i.e. inflammation, pain and hyperaemia), which subside with symptomatic management. Infection risk is very low.
In a few patients, the expected articular symptomatology improvement with radiosynoviorthesis is not seen. In such cases, the initial dose can be repeated 3–6 months later, according to the patient's clinical course. We usually repeat treatment between 6 and 12 months after the initial one and, for the repeat treatment, we always try to deliver a dose lower than that we injected the first time [41].

**Dosimetry**

Radioactive isotopes, when adequately handled by specialized personnel, do not carry risk for patients. DNA alterations and stochastic effects from radioactive isotopes, if any, are minimal. Results from studies carried out by the Department of Nuclear Medicine of our medical centre in collaboration with the Department of Dosimetry and Radioprotection show that the risk for systemic radiation and lethal cancer is minimal to nil. These results are in keeping with those from other authors [41–44]. Moreover, to our knowledge, no cases of malignancy attributable to the use of radioactive isotopes for radiosynoviorthesis have been reported, even in young patients.

**Cost**

At present, financial issues of both therapeutic and diagnostic procedures are of increasing concern within national healthcare systems. Isotope procedures are said to be costly. This is not true, particularly if compared to other medical and surgical procedures and if the cost–benefit relationship is considered. For instance, the cost of the most expensive radioactive isotope procedure for joint treatment (i.e. radiosynoviorthesis with $^{90}$Y) at the Department of Nuclear Medicine of our medial centre amounts to approximately 399.45 €. The cost estimation has been broken down as follows:

- **Personnel** 99.40 € = 93.33 US $ = 63.51 GB £
- **Material** 291.26 € = 273.49 US $ = 186.10 GB £
- **Overheads** 8.79 € = 8.25 US $ = 5.62 GB £
- **TOTAL** 399.45 € = 375.07 US $ = 255.22 GB £

In Spain today it is to estimate the cost of medical and surgical procedures based on the so-called relative value unit (RVU). When estimated RVUs for the different therapeutic and diagnostic procedures conducted at the Department of Nuclear Medicine of our medical centre, the RVU for radiosynoviorthesis with $^{90}$Y was 5.06.

At our Department of Nuclear Medicine, the RVU equal to 1 corresponds to bone scanning, which is the most frequently performed procedure. Therefore, the cost for radiosynoviorthesis with $^{90}$Y is only some five times higher than that for bone scanning.

**Conclusions**

Radiosynoviorthesis may be a cost-effective, cheap and safe alternative for surgical synovectomy in some cases of arthritis. As with any other radioisotope therapeutic procedures, beta radiation emitter radioactive isotopes are used, because of their low penetration power, low range and high local radiation power. The choice of the radioisotope to be used is based on the size of the joint to be treated; thus the smaller the joint, the lower the beta radiation penetration power the radioisotope selected should have. Thus, we use $^{90}$Y for the knee, $^{186}$Re for the elbow and ankle and $^{169}$Er for interdigital joints.

**References**


CHAPTER 12

Synoviorthesis in haemophilia


Introduction

A synoviorthesis consists of the intra-articular injection of a pharmacological agent with the aim of 'stabilizing' (orthesis) the synovial membrane of a joint (synoviorthesis). Synoviorthesis has been utilized for more than 25 years. Ahlberg [1] reported the use of intra-articular radioactive gold (198Au) in the haemophilia population in 1971, and many centres in the world have implemented programmes of intra-articular synovial control using yttrium-90 (90Y) and phosphorus-32 (32P). The use of gold and 32P have been approved by the Federal Drug Agency (FDA) in the USA and approval of 90Y and some other agents is pending.

Fernandez-Palazzi [2] reviewed his experience in the treatment of recurrent haemarthrosis and chronic synovitis by nonsurgical means. Experience with synoviorthesis with rifampicin and radioactive colloids was analysed, and a multiple chromosomal study to demonstrate safety of radioactive injections was described. The results obtained were adequately satisfactory to recommend synoviorthesis as the treatment of choice to prevent recurrent haemarthrosis.

Rodriguez-Merchan [3] stated that the goal of both synoviorthesis and surgical synovectomy is to remove the inflamed and hypervascular synovium as soon as possible in order to prevent the onset of haemophilic arthropathy (Figs 12.1 and 12.2). Ideally, these methods should be performed before the articular cartilage has eroded (Fig. 12.3). Radioactive synoviorthesis is an effective, relatively simple, virtually painless and comparatively inexpensive technique for the treatment of chronic haemophilic synovitis, even in patients with inhibitors. Thus, radioactive synoviorthesis is the best choice for patients with persistent synovitis. The current recommendation among orthopaedic surgeons and haematologists is that when three early consecutive synoviortheses (repeated every 6 months) fail to halt synovitis, a surgical synovectomy (open or arthroscopic) should be immediately considered [3].

Fernandez-Palazzi et al. [4] reported that radioactive synoviorthesis with 198Au, 90Y, rhenium-186 (186Re) or 32P would be appropriate treatment for recurrent haemarthroses in haemophilia. The clinical results, obtained by different centres, show a definite diminution of haemarthroses in 88% of cases [3]. The advantages of radioactive synoviorthesis compared with surgical synovectomy are: equivalent or better results; the requirement of substantially reduced antihaeomophilic factor; the possibility of performing the procedure on multiple joints concurrently on an ambulatory basis; much less discomfort for the patient; no loss in joint range of motion; and the low cost of the procedure.

Fig. 12.1 Clinical view of the knees of a young boy with haemophilia. Note the severe degree of haemophilic synovitis in his right knee.

Fig. 12.2 Histological view of chronic haemophilic synovitis. Note some collagen fibres stained with haemosiderin pigment (stain, Perl; magnification × 295).
In cases of failure, the procedure can be repeated after 6 months, and as many as three times on the same joint. Studies performed on the chromosomal changes that could be attributed to the radioactive material show the disappearance of these alterations a few years after treatment [4]. Despite over 40 years experience, there have been no reports documenting an increased incidence of neoplasia following radiosynoviorthesis.

**Intra-articular injection of corticosteroids**

Shupak et al. [5] were among the first to report satisfactory short-term results with the intra-articular injection of corticosteroids in haemophilia. Rodriguez-Merchan et al. [6] performed a pilot prospective study to investigate the role of the procedure, initially in the short term and later with long-term follow-up. The primary objective of the study was to investigate a less aggressive method for the treatment of haemophilic synovitis, given that the alternative procedures were synoviorthesis (intra-articular injections of radioactive materials) and surgical synovectomy (open or arthroscopic).

This prospective study evaluated the effectiveness of intra-articular methylprednisolone (80 mg) in 10 knees of 10 haemophilic patients with chronic synovitis. The patients were evaluated by radiographs and ultrasound before initiating treatment, and thereafter periodically for a 5-year follow-up period. One year after injection improvement in pain level was satisfactory, but pain recurred shortly thereafter. Five years after completion of treatment, all results were poor. Thus, it appears that injection of intra-articular methylprednisolone may be beneficial in relieving pain associated with arthropathy for up to 1 year but is not comparable to radiosynoviorthesis in reduction of haemarthrosis.

Fernandez-Palazzi et al. [7] reported that from 1966 to 1988, 34 patients with advanced chronic haemophilic synovitis (25 grade III and nine grade IV of their own scoring system) were treated with intra-articular injections of long-acting dexamethasone (sodium phosphate of dexamethasone plus acetate of dexamethasone) in cycles of three injections with 3-week intervals between each injection and 6-month rest intervals between cycles for as many as three cycles, depending on the evolution of each case. All patients had chronic severe synovitis, axial deformity, muscular atrophy and diminution of range of movement. The group included 31 knees, two ankles and two shoulders. Subjective and objective evaluations were carried out grouping the results in good, fair and poor categories according to patient satisfaction, presence of synovitis, pain, range of motion and limitation of activities of daily living. Subjective results included 19 good, 12 fair and four poor results. The objective evaluation showed 22 good, nine fair and four poor results at an average follow-up of 1.5 years. The use of intra-articular dexamethasone is an alternative in the short- to medium-term for treatment of advanced chronic haemophilic arthropathy with pain and limitation of function before resorting to surgical reconstruction.

**Chemical synoviorthesis**

The most commonly used chemicals have been osmic acid and rifampicin. In fact, they have been utilized as an alternative to radioactive agents because of lack of availability or fear of radiation as a potential source of malignancy. Salis et al. [8] retrospectively reviewed their experience with non-surgical synovectomy in the treatment of recurrent haemarthrosis with arthropathy in patients with von Willebrand’s disease, which is the most common inherited bleeding disorder, with an overall prevalence in the general population of 0.8–1.3%. Haemarthrosis occurs mainly in the most severe forms of the disease (type 3), with a frequency of 3.5–11%, and can cause severe arthropathy similar to that seen in haemophilia. Four of six patients had type 3 disease and the remaining two had type 2 disease. The age range was 13–63 years. The frequency of haemarthrosis prior to synovectomy was 1–4 per month. One (n = 2) or both (n = 1) knees were treated in four cases, one (n = 1) or both (n = 1) ankles in three cases and an elbow in one case. $^{90}$Y was used in a dose of 5 millicuries (mCi) (or 185 mega becquerels (MBq)) for one knee, $^{186}$Re in a dose of 2 mCi (or 74 MBq) for two ankles and the elbow and osmic acid for two knees and one ankle. Clinical and radiological results were evaluated 6 months after synovectomy using the World Federation of Haemophilia score. Radiological lesions remained stable and clinical manifestations improved in every case ($P < 0.05$). Five patients achieved a complete remission. Safety was satisfactory and there were no complications. The clinical efficacy of synoviorthesis, using radiocolloids or osmic acid in arthropathy caused by von Willebrand’s disease, seems similar to that in haemophilia.

Caviglia et al. [9] reported that, for many years, rifampicin has been used empirically for the treatment of chronic haemophilic synovitis with encouraging results. A clinical study was
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performed on 48 haemophilic patients (48 joints). Seventeen elbows, eight knees and 23 ankles were treated. The mean age of the patients was 6 years (range 4–23 years) and the mean follow-up was 29 months (range 24–53 months). Overall, 40 excellent and eight good results were obtained. The average number of weekly injections of rifampicin was 3.06 (range 1–10 injections). Eight patients experienced pain on the first injection, which subsided gradually with the subsequent procedures. Synoviorthesis with rifampicin seems to be a good method for the treatment of haemophilic synovitis, especially in small joints (elbows and ankles) and in younger children.

Caviglia et al. [10] reported on the experience of three Latin American centres with rifampicin and compared it to radioactive synoviorthesis results. Results indicated that chemical synoviorthesis with rifampicin is indicated in younger patients (< 15 years) and small joint (ankles and elbows). Fernandez-Palazzi et al. [11] also assessed the effectiveness of intra-articular rifampicin in haemophilic patients. Two hundred and fifty milligrams of rifampicin was injected into the elbow and ankle joints and 500 mg was injected into knee joints with 3–10 mL of lidocaine, depending on the joint size. The injections were repeated once a week for 7 weeks. Patients were only covered with antihaemophilic factor on the day of the injection at 30% above their coagulation level. The results were evaluated using subjective reports from the patient and objective assessment by the examiner. In the subjective reports the patient graded the results from their own perspective from 1 (poor) to 10 (excellent): 1–3 poor; 4–6 fair; 7–8 good; and 9–10 excellent. In the objective reports the grading was: excellent ('dry joint', full function, no haemarthrosis, no synovitis); good (clinical improvement, synovitis, reduction of haemarthroses, full function); fair synovitis (reduction of haemarthroses, no change in function); poor synovitis (persistent haemarthroses). This paper reports on the results of 38 patients with 39 joints with more that 3 years follow-up (mean 1.8 years). There were 22 knees, nine elbows and eight ankles. Subjectively, there were excellent results in 21 joints (11 knees, six elbows and four ankles), good results in 15 joints (eight knees, three elbows and four ankles), fair results in two knees and a poor result in one knee. Objectively, results obtained were excellent in 20 joints (11 knees, six elbows and three ankles); good in 17 (nine knees, three elbows and five ankles); fair in one knee and poor in one knee.

Radiosynovectomy

Today, synoviorthesis is the procedure of choice, and surgical synovectomy is performed only if a number of consecutive synoviortheses fail to stop or diminish the frequency of recurrent haemarthrosis [12]. The indication for synoviorthesis is chronic hypertrophic synovitis associated with recurrent haemarthrosis that does not respond to haematological treatment. Synoviorthesis should be performed under clotting factor coverage to avoid the risk of bleeding during the procedure. In patients with inhibitors, synoviorthesis can also be performed with minimal risk. In fact, the procedure is especially indicated in patients with inhibitors because of its ease of performance and low rate of complications compared to surgical synovectomy.

It is important to differentiate between haemarthrosis and synovitis. Acute haemarthrosis is associated with severe pain, and the joint is maintained in a position of comfort (typically in flexion). In contrast, chronic hypertrophic synovitis is not associated with as much pain. The synovium is palpable as a soft-tissue mass whereas a haemarthrosis will have a fluid characteristic. Before making the recommendation of a synoviorthesis, the diagnosis should be confirmed by radiographs, ultrasound and/or magnetic resonance imaging (MRI) (Figs 12.4–12.6). Radiographs should also be taken in order to assess the degree of haemophilic arthropathy at the time of diagnosis. In many situations, synovitis and haemarthrosis coexist.
Selection of the radioisotope should consider the half-life, because the intensity of the inflammatory reaction is directly related to the rate of exposure; and the size of the radiocolloid, the larger the size the less tendency for the material to leak from the joint space. The material should be a pure beta-emitting radioisotope, thereby minimizing the whole body exposure from gamma radiation. Taking into account the high cost and limited supply of these materials, it is best to schedule groups of 6–8 patients to perform radiation synovectomy. This will require some patients to wait upwards of 3–6 months until the whole group is scheduled for the procedure. If possible, patients should be maintained on continuous prophylaxis and therapeutic exercises while waiting for the procedure.

Synoviorthesis can be performed at any age in haemophilia patients. Performing an intra-articular injection in a very young child does pose the problem of patient co-operation which may require conscious sedation or even general anaesthesia. The potential of radiation-induced cellular damage or chromosomal abnormalities remain a concern, particularly in the child. After more than 30 years of experience in using radiation synovectomy, neither articular nor systemic neoplasia has been reported in the medical literature [3,4].

One possible, although rare, minor complication is a cutaneous burn if the radioactive material leaks out of the joint. These burns are small and superficial, healing in about 2 weeks without residual scar. This problem can be prevented by flushing the needle and needle tract with a mixture of Xylocaine and a depositing steroid solution as the needle through which the radiocolloid was injected and then applying pressure to the injection site. Another potential complication is an inflammatory reaction after injection, which can be managed with rest and non-steroidal anti-inflammatory drugs (NSAIDs). These reactions are less likely with longer half-life agents. Image intensifier or ultrasound-guided articular puncture is commonly used to avoid extra-articular injection of the radioactive material.

It is possible to perform multiple synoviorthesis in a single session. It is probably best to carry out no more than two injections at the same time to reduce the risk should any of the material escape. If two joints are to be injected, consider injecting two joints on the same side (i.e. an elbow and knee, elbow and ankle, knee and an ankle).

Molho et al. [13] reported on 116 chemical and 90 radioactive synovectomies performed between 1970 and 1994 on 107 patients with severe haemophilia and two with type 3 von Willebrand's disease. The products used were osmic acid in 100 cases, $^{90}$Y in 35 cases, $^{186}$Re in 48, erbiuin-169 ($^{169}$Er) in two, hexacetonide triamcinolone in 16 and $^{198}$Au in five cases. The use of radioactive colloids is not allowed in France in patients under 15 years of age. Twenty-nine patients had more than one synovectomy in the same joint. All patients were evaluated for 6 months postsynovectomy, using both a clinical and a radiological score. Six months after synovectomy, a good or excellent result was obtained in 81% of the joints treated with isotopes, compared with 44% of those treated with osteoarthritis. This superiority of isotopes over osmic acid was still observed after 6 months for the 89 joints that were re-evaluated, with follow-up ranging from 1 to 9 years. A radiological score was calculated in 84 cases. The best results were from joints with the lowest scores presynovectomy (< 7). No correlation could be established between the clinical and the radiological scores, because of the small size of the sample. Molho et al. concluded that chemical and radioactive synovectomy are simple and safe procedures for haemophilic arthropathy. In their series, the efficacy of isotopic synovectomy was greater than that of chemical synovectomy, and this benefit seems to persist after 6 months, and up to 9 years in the group of patients with longer-term follow-up.

Nuss et al. [14] studied the clinical, plain X-ray and MRI findings in 13 haemophilic joints previously treated with radiosynoviorthesis. $^{32}$P had been injected into the joints in an attempt to halt recurrent haemorrhage. Prior to $^{32}$P injection, the majority of joints demonstrated bone damage evident on plain X-ray, secondary to recurrent haemorrhage. At the follow-up evaluation they found plain X-rays were adequate to identify cysts, erosions and cartilage loss in these very damaged joints. MRI was superior to clinical examination and plain X-ray in identifying synovial hyperplasia and effusions. However, the persistence of synovial thickening did not correlate with the bleeding frequency and clinical result.

Matthew et al. [15] presented their experience beginning in 1993 with 11 paediatric patients who underwent 17 $^{32}$P isotopic synovectomies for chronic haemophilic arthropathy. $^{32}$P was injected into the joint per protocol, approved by the institutional review board. All patients were male. Nine were factor VIII- and two were factor IX-deficient. The following joints were treated: ankle ($n = 10$ procedures), elbow ($n = 5$) and knee ($n = 2$). The first procedure was performed in December 1993. Mean age at the first procedure was 10.8 years (range 5.2–15.2 years). Mean pretreatment joint clinical scores using the World Federation of Haemophilia guidelines for the ankle was 5.5.
analysed. Patients in this study group had a bleeding frequency
between 1988 and 2000. Results of 130 procedures
32
P chromic
who performed 170 radiosynovectomies using
90
Y synoviorthesis should be performed early, in
90
Y synoviortheses on 44 persons with haemophilia
of at least three episodes per month in a target joint and failed
conservative treatment, which included a combination of clot-
ing factor concentrate and physical therapy. The 115 primary
procedures, including 50 knees, 44 elbows, 14 ankles, five
shoulders and two subtalar joints, were followed for an average
of 3 years (range 0.5–11.6 years). The 15 repeat procedures,
including seven knees, six elbows and two ankles, were fol-
lowed for an average of 2.7 years (range 0.5–7.2 years). The
average postprocedure bleeding frequency reduction, includ-
ing primary and repeat procedures, was 70%. For primary pro-
cedures, excellent and good results (haemarthrosis reduction
from 75 to 100%) were obtained in 79.2% of cases at 6 months
to 8 years. For repeat procedures a combination of excellent
and good results were obtained in 62.4% of cases at 6 months
to 3 years. Regression analysis showed no correlation between
results in terms of bleeding reduction, and age or degree of
arthropathy. Radiation was well contained within the joint
and there were no observed or identified complications. The
authors concluded that the procedure is effective, safe and
highly cost-effective in comparison to open surgical or arthro-
scopic synoviectomy.

Lofqvist et al. [19] reported on nine patients with haemop-
ophilia and clotting factor inhibitors (six with haemophilia A,
three with haemophilia B). Nineteen joints were treated with
radioactive synoviorthesis using 198Au. Ages ranged from 3 to
40 years. Synoviorthesis was performed when the antibody
titre was low (< 10 Bethesda units), thus making haemostasis
possible by factor administration for 2–4 days. On five occa-
sions, radioactive synoviorthesis was performed simulta-
neously with tolerance induction according to the Malmö
protocol. A bleeding-free interval of more than 6 months was
obtained in 11 joints, six of which remained haemarthrosis-free
for more than 1 year. At long-term follow-up (range 18–182
months) five joints were rated good, one joint was fair and
11 joints were poor. Although the results were inferior to those
for patients with haemophilia without inhibitor, radioactive
synoviorthesis should be considered because of its ease of per-
formance and the definite decrease in joint bleeding frequency
that it brings about. This is of particular interest in patients
with haemophilia caused by factor inhibitor who otherwise are
difficult to treat.

Falcon de Vargas and Fernandez-Palazzi [20] assessed chro-
mosomal structural changes (CSCs) studied by conventional
lymphocyte cultures and banding techniques in 79 haemophilic
patients with haemarthrosis treated with radioactive synovi-
orthesis, 31 haemophilic patients with haemarthrosis not
treated by this procedure and 110 non-haemophilic patients
matched by age and sex (control group). In 14 patients treated
with 198Au (group A), premalignant CSCs and non-specific
CSCs were found in 1.69 and 17.23% of metaphases, respecti-
vely. The former disappeared, but 1.7% of the non-specific
changes persisted 2 years after injection. In 31 patients treated
with 186Rh (group B), CSCs were not found previous to radio-
active synoviorthesis but were present as non-specific changes
in 1.25% of metaphases 6 months later; they disappeared
1 year after injection. In 34 patients treated with \(^{90}\)Y (group C), CSCs were not found previous to radioactive synoviorthesis but were present as non-specific changes in 0.89% of metaphases 6 months later; they disappeared 1 year after injection. Only non-specific CSCs were found in 0.79% of metaphases in haemophilia patients not treated with radioactive synoviorthesis (group D). CSCs were not present in control subjects. The authors concluded that in some haemophilic patients with haemarthrosis treated with radioactive synoviorthesis using \(^{198}\)Au, \(^{186}\)Rh or \(^{90}\)Y, reversible premalignant or non-specific CSCs could be present; non-specific CSCs may persist in a low proportion of metaphases up to 2 years after injection when \(^{198}\)Au is used as the radioactive agent. \(^{198}\)Au is both a beta and gamma emitter. Radioactive synoviorthesis with a pure beta emitter seems to be, from a cytogenetic point of view, a safe alternative for these patients.

**Alternatives to synoviorthesis**

Rodriguez-Merchan et al. [21] reported a prospective study carried out from 1974 to 1996 to determine optimal treatment for chronic haemophilic synovitis of the knee and synovitis of the elbow. Sixty-five patients with synovitis affecting 65 knee joints and 40 patients who had synovitis of the elbow (44 elbows), despite a 3-month trial of prophylactic substitution therapy, were treated by synovectomy. Radiation synovectomies (\(^{198}\)Au synoviorthesis) were performed on 38 knees, open surgical synovectomy on 18 and nine had an arthroscopic procedure. Radioactive gold synoviorthesis was performed on 29 elbows, and 15 had a resection of the radial head and partial open synovectomy. Synovectomy (by any method) significantly reduced bleeding episodes, but did not halt the radiographical deterioration of the joints. It is thought that radiation synovectomy is the best choice for patients with persistent synovitis of the knee and elbow unresponsive to a 3-month trial of prophylactic factor replacement. If two to three consecutive synoviortheses with 3–6 months intervals had been ineffective, or when the radiographical score is more than two points, a surgical synovectomy is indicated.

When chronic synovitis is allowed to persist, the membrane can hypertrophy to the point where it cannot be adequately ablated by a pure beta-emitting radiocolloid, which only penetrates about 5 mm. In these cases as well as those in which repeated radiosynoviorthesis has failed, arthroscopic synovectomy is often effective [22].

**Conclusions**

Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage; which, based on many studies, is irreversible.

It can also be used in patients with inhibitors with minimal risk of complications. On average, synoviorthesis has a 75–80% satisfactory outcome in the long term. From the clinical standpoint, such efficacy can be measured by the decrease in the number of haemarthroses, with complete cessation for several years in some cases. One should bear in mind that in 20–25% of cases, synoviorthesis fails to control haemarthroses. In such cases, it can be repeated. Global results of treatment with chemical synovectomy (osmic acid and rifampicin) seems to be less favourable than with radionuclides (\(^{90}\)Y and \(^{32}\)P) [16–18,22]. In cases where the synovium is thicker than 5–10 mm, and haemarthroses persist following synoviorthesis, arthroscopic synovectomy is indicated.

**References**


Oxytetracycline chlorhydrate as a new material for chemical synoviorthesis in haemophilia

F. Fernandez-Palazzi, R. Viso, R. Bernal, G. Capetillo and H. Caviglia

Introduction

Haemarthrosis is the most frequent bleeding episode in haemophilia, with 83% of patients affected. It is one of the most common and disabling problems in haemophiliacs. Treatment depends on many factors such as the severity of the bleeding, grade of joint affection and, in some countries, on the availability of resources for treatment. Synovectomy is an accepted procedure for treatment of those target joints with recurrent bleeding in haemophilic patients. The aim of the treatment is to stop the bleeding that comes from the subsynovial venous plexus by resecting or fibrosing the hypertrophic synovium to prevent further damage and restore function. This can be accomplished by removing the synovial tissue with surgery [1], radiocolloids [2] or chemical agents [3,4]. In our centre we have chosen the latter as standard treatment with great success, which has been reported in previous papers [3,4].

Treatment of recurrent haemarthrosis

In order to prevent haemarthrosis we must act directly on the synovial membrane either by surgical resection—synovectomy [1,5]—or, preferably, by producing fibrosis of the synovium and subsynovial plexus—synoviorthesis. Synoviorthesis can be performed chemically with osmic acid, but is very painful, or, preferably, by rifampicin [3,4], which produces a sclerosis of the synovium by its fibrotic and antifibrinolytic action, thus strangling the bleeding vessels. The use of a radioactive colloid has been the material of choice for synoviorthesis [2,5] but the disadvantage of using radiocolloids in developing countries is their cost and requires, in some countries, the colloid to be imported, thus increasing cost and quantity of dosage to be bought because of the diminution of activity for its mean life time.

Surgical synovectomy, first reported in haemophilia by Storti et al. in 1969 [1], as in any surgery performed in haemophilia, requires a large amount of antihaemophilic factor (AHF) in order to increase the deficient factor on the day of surgery up to 100%, above 50% for the first week and up to 30% up to the fourth week postoperatively, plus an intensive rehabilitation programme to avoid postoperative stiffness, and hospitalization is necessary. Most authors reporting on results of surgical synovectomies in haemophilia [1,5–7], found 80% of cases with great improvement in or no recurrence of haemarthrosis, but with a variable postoperative restriction of range of movement.

Different centres utilize different classifications for indicating synoviorthesis. For practical purposes we classify haemophilic arthropathy into four degrees or stages depending on the clinical severity of the arthropathy facilitating the indication of synoviorthesis (Table 13.1). We (F. Fernandez-Palazzi et al.)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Synovial Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Transitory synovitis</td>
<td>With return to prebleeding situation after haemarthrosis subsides. In these cases synoviorthesis is indicated preventively when there are more than three haemarthroses in 6 months</td>
</tr>
<tr>
<td>Grade II</td>
<td>Permanent synovitis</td>
<td>After haemarthrosis subsides chronic synovitis persists, with enlargement of the joint and muscular hypertrophy. In these cases synoviorthesis is elective</td>
</tr>
<tr>
<td>Grade III</td>
<td>Chronic stage</td>
<td>Besides grade II synovitis there are axial or rotational deformities of the limb, with diminution of range of motion and pain. Synoviorthesis will be of recourse. Indicated treatment with long-acting corticosteroids and/or hyaluronic acid</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Osseous or fibrous ankylosis</td>
<td>Synoviorthesis is not recommended but treatment with long-acting corticosteroids and/or hyaluronic acid</td>
</tr>
</tbody>
</table>
introduced in 1989 [3] the use of intra-articular rifampicin that acts on the synovial membrane, via its fibrosing properties, sclerosing it and thus reducing haemarthrosis. The dosage used for knees is rifampicin 500 mg injected intra-articularly with 10 mL lidocaine once a week for 5–7 weeks, depending on the results obtained. Patients were only covered with AHF up to 30% on the injection day. Our satisfactory results [3,4] made this material the one used in our centre until the introduction of oxytetracycline clorhydrate. Because it has been very difficult lately to obtain rifampicin in ampoules, we were compelled to find another material with similar fibrotic action.

**Synoviorthesis with oxytetracycline clorhydrate**

We (FFP) started searching for other material that could have fibrosing activities similar to rifampicin. Thus, the Caracas team searched the literature on materials used by pneumologists in order to perform pleurodesis, because the material they require in order to perform this procedure is similar to that required for synoviorthesis (Aquiles Ermini, Centro Médico de Caracas, 10 August 2000, personal communication). The materials used in such cases are: talcum [9,10], bleomycin [11], Corynebacterium parvum [12], fibrin glue [13,14], iodopovidone [11], tetracycline [15] and sodium hydroxide [16,17]. For its effectiveness, facility in dosage and the capability of fibrosing in smaller quantities of solution we finally chose oxytetracycline clorhydrate [18].

This is a broad-spectrum antibiotic, active in both Gram-positive and Gram-negative bacteria, especially filarias and rickettsias. In intravenous injections it was noted that phlebitis developed because of its irritative property. This antibiotic was withdrawn from human use as a result of this irritating action when injected intravenously, and is now only used for veterinarians purposes. Having been previously registered for human use, we informed representatives of the Ministry of Health of the present use as a fibrotic agent to be used intra-articularly. This irritating action is what we were searching for, in order to produce fibrosis of the synovial membrane.

Oxytetracycline clorhydrate, Emicina® (Pfizer), comes in 20 and 100 mL bottles, with a dose of 50 mg of active material per mL of product (Fig. 13.1). Not having been used previously for synoviorthesis, we had to develop the dosage regimen required for each joint. The dosage developed by our Unit was as follows:

- **knees**: 5 mL Emicina (250 IU) plus 7–10 mL anaesthetic, according joint size;
- **elbows**: 2 mL Emicina (100 IU) plus 2 mL anaesthetic; and
- **ankles**: 1 mL Emicina (50 IU) plus 1 mL anaesthetic.

When this study was started, and because the drug to be injected was a veterinary drug, the first patients were informed why we switched from rifampicin to oxytetracycline and that this drug, for the above reasons, was only found in its veterinary presentation. Because of the beneficial results obtained at that time, all future patients agreed to use it and compelled us to proceed further with the treatment.

At the time we had in process an experiment in rabbits to demonstrate its benefit on experimentally induced haemarthrosis, with the assistance of Raul Rojas and Francisco Salcedo, residents of our Unit who performed this work as their graduating thesis [19]. We used a scientific method to analyse the experimental action of Emicina (oxytetracycline clorhydrate) on the synovial membrane on rabbits with haemarthrosis, taking into consideration that synovial tissue is formed by an epithelial tissue composed of one layer of synoviocytes, resting on its own plate of lax connective tissue well irrigated by vascular tissue.

Histologically, we have reparation when the defect on the tissue is covered by a different one; and regeneration when the defect on the tissue is covered by one similar. We used 26 rabbits and we injected homologous blood on the left knee of the rabbit twice weekly for 2 weeks. The blood was obtained from an adult rabbit by heart puncture. After 2 weeks, two rabbits were sacrificed to observe intra-articular alterations, and the rest of the rabbits were grouped into two groups: group A (eight rabbits) received 1 mL intra-articular saline solution once a week for 4 weeks; group B (16 rabbits) received 1 mL (50 mg) intra-articular Emicina on the left knee once a week for 4 weeks. All group B rabbits showed similar histopathological alterations (regeneration), different from group A (reparation).

The experimental action of Emicina on rabbit synoviorthesis after haemarthrosis, developed regeneration of the synovial tissue and controlled reparation, with slide enlargement of synovial tissue, less irrigated, and less prone to bleed. Once the experimental model showed an enlargement of the synovial membrane with less irritation, thus less prone to bleed, we...
continued with our procedure, it being at present, in our opinion, the material of choice for chemical synoviorthesis.

**Materials and methods**

We performed a prospective non-controlled clinical study on chemical synoviorthesis with oxytetracycline clorhydrate (Emicina®) in 53 haemophiliacs on 54 joints. Of these haemophiliacs, we injected 31 knees, 15 elbows and eight ankles. According to grade these were: Grade I, 11 knees, nine elbows and five ankles; Grade II, 16 knees, six elbows and three ankles; and Grade III, four knees. Age ranged from 2 to 37 years with a mean of 14.5 years. Follow-up was from 1 to 11 months with a mean of 7 months. Dosage of product was:

- **knees**: 5 mL Emicina plus 5 mL anaesthetic;
- **elbows**: 2 mL Emicina plus 2 mL anaesthetic; and
- **ankles**: 1 mL Emicina plus 1 mL anaesthetic.

Mean injections were three (once a week), with a minimum of one injection and a maximum of seven doses in one case. Two cases were failures and required minimal surgical synovectomy.

Evaluation was made according to subjective and objective scale: pain from 0 (no pain) to 10 (pain requiring medication); range of movement (ROM) from 0 (no movement) to 10 (complete ROM); use of limb from 0 (impossible to weight bear) to 10 (normal use in daily activities). Objective evaluation was made by measuring ROM and diameter of joint. Thus, for pain, we obtained a diminution from 5.6 points previously to 0.5 points after treatment. Mean mobility was 5.5 with an increase of ROM. Patient satisfaction, despite some failures, was above 90%. Thus, we strongly recommend the use of oxytetracycline clorhydrate (Emicina) as the material of choice for chemical synoviorthesis because of its effectiveness, easy procedure and low cost.

**Conclusions**

We have reported the results of a multicentre study on the use of oxytetracycline clorhydrate (Emicina, Pfizer) as a new material for chemical synoviorthesis in haemophilic haemarthrosis in 54 injected joints. The results obtained according to a subjective evaluation scale that we created and the objective evaluation by the physician has been very satisfactory. In spite of the short follow-up and the small number of patients, for us the very satisfactory results make oxytetracycline clorhydrate the material of choice for chemical synoviorthesis in haemophilia because of low cost, easy availability, procedure and effectiveness.

In spite of these being early results, they are very satisfactory, especially in relation to pain, diminution of joint diameter and increase of ROM. Patient satisfaction, despite some failures, was above 90%. Thus, we strongly recommend the use of oxytetracycline clorhydrate (Emicina) as the material of choice for chemical synoviorthesis because of its effectiveness, easy procedure and low cost.

**References**


Introduction

The presence of chronic hypertrophic synovitis in the joint of a person with haemophilia is the result of recurrent haemarthroses, and the cause of a chronic arthropathy that leads to severe functional impairment. The acute bleeding episode initiates the onset of a series of recurrent haemarthroses leading to chronic hypertrophic synovitis. Considerable effort over the past 30 years has been placed on attempting to control the acute bleeding episode, thereby preventing recurrent haemarthroses. Early aggressive on-demand factor replacement for acute haemarthrosis significantly reduced the incidence and severity of chronic haemophilic arthropathy; however, it has not totally prevented the recurrence of bleeding episodes which accounts for why chronic synovitis remains a problem. The only treatment method that has been successful in preventing joint bleeds is a prophylaxis programme instituted early in the person’s life prior to joint bleeding. This method of treatment is very limited because it takes enormous resources to provide such a treatment protocol. Unfortunately, even on-demand factor replacement for acute haemarthrosis is not available in many parts of the world. This leaves many people with haemophilia still at risk for developing chronic hypertrophic synovitis secondary to recurrent haemarthroses. Once chronic hypertrophic synovitis is present, the most effective method of treatment has been some form of ablative procedure to either remove or destroy the synovium.

Review of the literature

Open surgical synovectomy for haemophilic arthropathy was first performed by Storti in 1966 and reported on in 1969 [1]. This report was encouraging because of the improvement in joint function and a significant decrease in the number of recurrent haemarthroses. Since this initial report of open surgical synovectomy, other authors have reported similar results [2–6]. All of these reports suggest that there is a decrease in recurrent haemarthroses. However, these reports plus additional publications [7–16] state that one of the main problems associated with this procedure is the risk of loss of joint motion.

As the arthroscopic procedures developed in the 1970s, one of the main benefits recognized was less postoperative morbidity following arthroscopic surgery as compared to open surgical procedures of the joints, particularly the knee. Because of this potential benefit of arthroscopic surgery, the technique of arthroscopic synovectomy was attempted for chronic haemophilic arthropathy and first reported by Kim et al. [17] and Wiedel [18] at the World Federation of Haemophilia Congress in Stockholm, Sweden, in 1983. The results of these cases were published by Wiedel [19] in 1985 and Klein et al. [20] in 1987, both reporting satisfactory results from the standpoint of a significant reduction in recurrent haemarthroses and decreased morbidity with preservation of joint mobility and shorter hospital stay.

Triantafylion et al. [21] in 1992 reported a comparison of eight open to five arthroscopic synovectomies of the knee. The results clearly demonstrated the benefit of the arthroscopic technique, with improved range of motion and an easier postoperative recovery. Wiedel [22] in 1996 reported on a 10–15-year follow-up of his original arthroscopic synovectomies. Nine cases were followed for this length of time and the procedure was successful in maintaining a decrease in the incidence of haemarthrosis. Also, range of motion remained satisfactory, with only one patient losing significant motion because of a severe postoperative haemarthrosis. Radiographical evaluation of all of these knees demonstrated progression of the disease process including narrowing of the cartilage space; however, none of these cases required any additional operative procedures. The conclusion from this study showed that the arthroscopic synovectomy was successful in controlling recurrent haemarthrosis and probably slowed, but did not halt the progression of the haemophilic arthropathy. Teigland et al. [23] reported a 6–21-year follow-up on 16 patients who underwent synovectomy for haemophilic arthropathy. There were a total of 21 synovectomies: nine knees, six ankles and six elbows. This report demonstrated that synovectomy was efficacious in reducing recurrent haemarthroses and joint pain. The total range of motion was not improved, but functional range was improved.

Eickhoff et al. [24] in 1997 reported 32 knee arthroscopic procedures performed over a period between 1988 and 1991. These
This procedure may have considerable benefit in the control of chronic synovitis. Although only three cases were performed, postoperative haemarthrosis. In an attempt to avoid the actual mechanical device. This leaves a surface at risk for bleeding which explains why a frequently reported complication is a postoperative portal haematomas. Cohen et al. have been reported in two separate publications. Heim et al. in 1992 reported the development of an arterial venous fistula after an arthroscopic procedure for impingement symptoms. At the time of this procedure, 14 years postoperative synovectomy, Grade 3 articular and meniscal cartilage changes were observed. No synovial hypertrophy was seen. The three patients have not reported any recurrent haemarthroses in the affected knee.

Complications specifically related to arthroscopic surgery have been reported in two separate publications. Heim et al. in 1999 reported on two cases of expanding arthroscopic portal haematomas. Cohen et al. in 1992 reported the development of an arterial venous fistula after an arthroscopic synovectomy.

The technique of arthroscopic synovectomy utilizes mechanical devices in which the synovium is removed by a cutting device. This leaves a surface at risk for bleeding which explains why a frequently reported complication is a postoperative haemarthrosis. In an attempt to avoid the actual mechanical excision of the synovium, Menart et al. [29] reported on the use of holmium : YAG laser technique with the aid of the arthroscope. Although only three cases were performed, postoperative blood loss was minimal, and joint mobility rapidly returned. This procedure may have considerable benefit in the control of chronic synovitis.

**Discussion**

An update on the original nine patients reported by Wiedel in 1996 [22] giving a 15–20-year follow-up, reveals that six patients have died from AIDS, leaving three patients living. Of these three, one patient has required a total knee replacement because of progressive arthropathy. This patient was 34 years of age at the time of the arthroscopic synovectomy. The knee already had advanced arthropathy (Stage IV). Another patient underwent an arthroscopic procedure for impingement symptoms. At the time of this procedure, 14 years postoperative synovectomy, Grade 3 articular and meniscal cartilage changes were observed. No synovial hypertrophy was seen. The three patients have not reported any recurrent haemarthroses in the affected knee.

Arthroscopic synovectomy has been shown to be an effective method of surgically excising synovium. It has provided a significant reduction in recurrent bleeding episodes as well as maintaining a functional range of motion. However, this procedure is technically demanding; it requires considerable resources, not only from the standpoint of surgical equipment and expertise, but it also requires adequate factor concentrate replacement during surgery, and for an extended period postoperatively to control postoperative bleeding.

Other methods of controlling recurrent haemarthroses and persistent synovitis without surgical excision have been successful. These techniques include using radioactive materials. The Rocky Mountain Haemophilic Treatment Centre was approved for the use of isotopic synoviorthesis using 32P in 1993. Since that time, we have used the radioactive synoviorthesis method to manage chronic synovitis. This method has been extremely successful. In fact, since we began using the radioactive material, I have not had to perform a surgical synovectomy, either open or arthroscopic for a patient with haemophilia. This brings us to the issue of where does arthroscopic synovectomy fit into the treatment of chronic synovitis in a person with haemophilia.

At this time, I would consider arthroscopic procedures for managing internal derangement problems, but would not consider it as the first line of approach for treating chronic synovitis and controlling recurrent haemarthroses. There may be a need to consider arthroscopic synovectomy if alternative methods such as the radioactive synoviortheses have failed.

**Conclusions**

Based on experience over the last 20 years with arthroscopic synovectomy, there is clear evidence that this procedure is effective in removing the synovium. It does control recurrent haemarthroses, and has maintained a good functional range of motion. However, there is evidence of radiographical progression of arthropathy. This can be explained on the basis of irreversible articular cartilage changes already present at the time of the arthroscopic synovectomy. I believe that because recurrent bleeding episodes have been significantly decreased, and in some cases completely stopped, the progression of the arthropathy has been slowed.

**References**

THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES


Moderate haemophilic arthropathy
CHAPTER 15

New concepts regarding articular cartilage preservation in persons with haemophilia

M. Heim and T. Wallny

Introduction

Haemarthroses are a common occurrence in persons with haemophilia and the gold standard of management comprises the initial infusion of the missing coagulation factor, and local joint management using rest, immobilization, compression and elevation (RICE). Rehabilitation physical therapy programmes have been instituted early in order to allay muscle wasting and joint range of motion loss. Synovial hypertrophy, as a result of recurrent haemarthroses, has been recognized as having a detrimental effect upon the joint and where conservative haematological and orthopaedic managements have failed to control the synovial hypertrophy, synovectomy has been recommended.

Synovial tissue secretes proteolytic enzymes and it has been postulated that these enzymes destroy the articular cartilage. What has been noted is that in many patients, even after timely synovectomy, progressive clinical and radiological joint destruction continued. The intention of this chapter is to highlight a hypothesis that may explain the pathogenesis of these observations and suggest possible therapeutic avenues that may assist in joint preservation.

Hypothesis

In order to appreciate the pathological changes occurring within articular cartilage, a basic understanding of the structure and physiology of articular cartilage is necessary. Cartilage is produced by chondrocytes wherein elaborate molecular chains are constructed. Upon a central rod comprising about 2000 amino acids called hyaluronan, side chains are connected. These side chains consist of keratan sulphate and chondroitin sulphate (proteoglycans). Both these substances have strong negative charges and hence attract water. The entrapment of water provides cartilage with its shock-absorbing properties. Hyaluronan is not only an integral part of cartilage structure but it is also present within the synovial fluid. The hyaluronan has many attributes contributing to shock absorption: articular cartilage surface protection from friction forces, free radicals and inflammatory agents.

Extensive work has been published [1] dealing with the effects of blood upon articular cartilage. What has become apparent is that free blood, within the joint space, affects the cartilage. This detrimental effect was explained in terms of proteolytic enzymes that are released in response to the free blood. The proteolytic enzymes not only acted upon the free blood in the joint, but also affected the articular cartilage. In order to gain access to the articular cartilage surface it has been noted that the hyaluronan became depolymerized and fragmented, losing its previous intra-articular protective functions. It has been suggested by Stein and Duthie [2] that iron deposition, within the cartilage, has a detrimental effect. Recent studies have shown that the presence of blood around the cartilage causes the inhibition of proteoglycan production [3]. The time period of this inhibition is far longer than the clinical observation of haemarthrosis absorption and this seriously challenges the present policy of early physical therapy instigation. It becomes incumbent upon the therapist to weigh up the pros and cons of joint and muscle mobilization in the light of the temporary inhibition of proteoglycan production.

Being cognizant of articular cartilage and synovial fluid structure, attention has been paid to the provision of the cartilaginous components. The market is inundated with products containing chondroitin sulphate and glucosamine. These may be taken orally and, in addition, there are readily available products for intra-articular injection of sodium hyaluronate, which is a natural polymer of glycosaminoglycans. By the intra-articular injection of hyaluronate, theoretically the synovial fluid is temporarily reconstituted, thus providing protective properties.

A small series was conducted in Bonn by Wallny et al. [4] and in Athens by Provelengios et al. [5]. In Wallny’s series beneficial findings were noted for over 30 months and these included less pain, and the ability to walk longer distances and climb stairs. The authors noted that the continuous beneficial effects, for as long as 2 years, could not be related to hyaluronate alone.
Provelengios et al. noted that the patients reported less pain and that the joint range of motion increased. In both series the patients were intra-articular injected once weekly for 5 consecutive weeks. The beneficial results of intra-articular hyaluronate injections have been reported in the literature [6–9]. Its applicability to patients with haemophilia or other joint bleeding disorders has not yet been established with long-term follow-up, but it was noted by Wallny et al. that, ‘with cartilage largely destroyed, never the less a positive effect on joint function can be achieved’. We have not found any double blind series comparing the efficacy of oral therapy to intra-articular therapy and no long-term follow-up studies showing that viscosupplementation therapy prevents the progression of affected articular end-stage haemophilic osteoarthropathy.

Two critical issues require elucidation.

1 Can articular cartilage be preserved/protected/reconstituted by the provision of the present marketed products? Several authors have published the beneficial results of oral viscosupplementation. Das et al. [10] reports that 4–6 months of treatment contributes to the pool of glycosaminoglycan (GAG) in cartilage and provides an inhibitor to synovial degradative enzymes. Lippiello et al. [11] reported that glucosamine and chondroitin sulphate supplementation ‘act synergistically in stimulating chondrocyte proteoglycan synthesis’. Leffler et al. [12] reported that both glucosamine and chondroitin sulphate have been shown to decrease osteoarthrisit symptoms severity. In a review article, Reginster et al. [13] stated that glucosamine sulphate could be a disease-modifying agent in osteoarthritis. One may question the dangers and the expenses incurred in the intra-articular injection of these agents but it would appear from the evidence provided that beneficial effects may be gained from either form of viscosupplementation.

2 Cognizant that intra-articular blood causes temporary proteoglycan produciton inhibition, one needs to query when and what sort of physical therapy programme should be instigated in order to safeguard against summatng an additional insult on the articular cartilage? The answer to this question is of paramount importance but it is beyond the scope of this chapter. Whether weight-bearing or not, the joint movements result in friction between the opposing cartilaginous surfaces and, without the ability to replenish the destroyed cartilage, further damage to the articular surfaces must be inevitable. The loss of congruity of the cartilage cannot be seen on radiographs. One needs to query whether immobilization and isometric muscle rehabilitation/preservation is not preferable to early mobilization?

Conclusions

Recent studies have shown that blood inhibits proteoglycan production in cartilage for an extended period. This chapter hypothesizes that proteoglycan inhibition is a possible explanation of joint deterioration postsynovectomy, and questions present physiotherapy protocols. Viscosupplementation has become popular as a modality for the preservation/replenishment/repair of damaged articular cartilage and numerous studies have shown the beneficial effects.

This chapter challenges older and established therapeutic protocols and hence it has been presented as a hypothesis. It would be appropriate to quote Jean Piaget, the nineteenth century Swiss philosopher, psychoanalyst and developmental psychologist: ‘the principal goal of education is to create men capable of doing new things’.

References


Knee malalignments in haemophilia: osteotomies

T. Wallny, A. Saker, H.H. Brackmann, C. Nicolay and C.N. Kraft

Introduction

A physiological configuration of the lower extremity is based on a correct anatomical axis, stable ligaments and a precise muscular interaction between agonists and antagonists. In haemophilic arthropathies deformities of the knee and hip joint are frequently observed, probably associated with mechanical overloading of the joint as a result of muscular malfunction and secondary loss of the ideal biomechanical axis [1]. This pathological mechanism is supported by increasing ligament insufficiency, resulting in joint instability, which ultimately facilitates the haemophiliac’s tendency to bleed into the joint.

In view of the progressing degenerative changes subsequently observed in the afflicted haemarthropathic joints, early joint replacement with alloplastic materials is propagated. Because of the often relatively young age of patients and the limited life span of artificial joints, this may not always be the ideal treatment. Osteotomies, with correction of the anatomical axis and preservation of the original joint, seem to be a feasible alternative. Joint replacement may hereby be avoided or at least postponed to a later stage of life. These two methods of surgical treatment for the arthropathic joint do not stand in competition to one another but should rather be understood as being complementary [2].

Criteria and indications for an osteotomy vs. joint replacement in the haemarthropathic joint do not markedly differ from those consigned to osteoarthrosis, and are [2]:

- biological age and life-expectancy of the patient;
- the ability to partially weight-bear;
- the patient’s body weight;
- bone quality (is a stable osteosynthesis possible?);
- stability of ligaments/tendons;
- degree of malalignment (deviations of more than 25° are more prone to cause intraoperative and neurological complications);
- preoperative range of motion (ROM); and
- patient’s profession and level of expectancy/demands.

When deciding for or against joint replacement in the haemophilic patient, we believe age to be of primary importance. With osteotomies being an alternative specifically for the younger patient, we would like to present long-term results of this method.

Materials and methods

Patients

From 1974 to 1984 we performed 52 corrective osteotomies in the vicinity of the knee joint on 48 haemophiliacs at our university hospital. Forty-five of these osteotomies (42 patients) were followed up postoperatively, on average 11.6 years (minimum 1 year, maximum 24 years) after the surgical procedure. The average age of the patients (40 patients with haemophilia A, two patients with haemophilia B and a factor activity of < 1%) at the time of surgical intervention was 31 years (minimum 15 years, maximum 49 years). In 25 procedures a varus deviation was corrected, while the remaining 20 procedures were performed because of genu valgum. Twenty-six procedures were performed on the right side, the rest on the left. For the varus correction, 24 high tibial osteotomies and one supracondylar osteotomy were performed, while for valgus correction eight high tibial osteotomies and 12 supracondylar corrective osteotomies were necessary. The degree of correction lay between 10° and 30°.

So as to compare the results of the operative intervention over a defined time period we also specifically assessed patients who had a postoperative follow-up of at least 5 years. In 32 patients (32 procedures) data was complete and in these we were able to compare results 1 and 5 years after surgical intervention to the preoperative status. The degree of correction lay between 10° and 30°. Genu valgum malalignment (n = 13) showed an average preoperative value of 12°, while genu varum malalignment (n = 19) showed an average preoperative value of 2°.

Surgery and postoperative treatment

The high tibial osteotomy was performed following the technique described by Coventry [3] and was stabilized using staples (Figs 16.1 and 16.2), while supracondylar osteotomies were fixated with an Association for the Study of Internal Fixation (ASIF)-condyle blade plate and screws according to the statutes recommended by the ASIF [4]. All high tibial osteotomies were treated with a plaster tutor over 6 weeks postoperatively. Patients were asked to partial weight-bear no more than 5–10
kg on the operated limb in this time. Six weeks after surgery an X-ray was performed and in cases of sufficient bony bridging the plaster was removed and training under physiotherapeutical observation ensued. In general, full weight-bearing was possible 12 weeks after the corrective osteotomy.

Clinical results were assessed by using the section ‘clinical examination’ and ‘pain’ of the Advisory Committee of the World Federation of Haemophilia (WFH) Score [5], while roentgenographical results were evaluated using the Pettersson Score [6]. The average preoperative WFH score for the treated knee was 6.3 points and the average preoperative Pettersson Score was 7.7 points.

Results

The average WHF Score at the time of follow-up (11.6 years postoperatively) improved by 2.2–4.1 points (SD 2.0 points). Thirty-eight patients improved, five patients deteriorated and two patients remained unchanged postoperatively. Some more important individual aspects of the score are presented as follows.

The frequency of synovial swelling markedly decreased postoperatively and was only found in three of 14 knee joints that had initially presented this symptom. Of 34 thighs that had preoperatively shown measurable muscular atrophy, this was postoperatively found to be persistent in only two cases. On average, thigh extensors showed an increase of strength measuring 3.5 Kp (kiloponds) (maximum 6 Kp, minimum 0 Kp).

At follow-up, 23 limbs showed that the measured axis was still in the physiological range. In genu valgum the angle of the femoral shaft to that of the tibial shaft improved from an average preoperative 12° (minimum 15°, maximum 10°) to 7° (minimum 3°, maximum 8°) postoperatively. Varus deformities were improved from an average 2° varus (minimum 5° varus, maximum 2° valgus) to 4° valgus (minimum 2° varus, maximum 5° valgus) postoperatively.

The range of motion (ROM) of the treated joints could not significantly be improved by the operation. While those knees ($n = 4$) demonstrating a preoperative normal to 10% decrease of normal ROM remained unchanged after surgery, we did find a postoperative change for those patients who showed an initial reduction of ROM between 10 and 30% ($n = 18$). One patient (1/18) showed marked benefit from surgery, 8/18 remained unchanged and 9/18 patients did in fact show some degree of deterioration at the long-term follow-up. Patients in the third category with a preoperative ROM of less than 30% of normal ROM ($n = 23$) showed a postoperative improvement in two cases (2/23) while 21 cases (21/23) remained unchanged (Fig. 16.3).

A preoperative flexion contracture of more than 15° was found in 16 knees (16/45). Of these, 7/16 could be improved
patients who survived at least 5 years after the surgical procedure \((n = 32)\) were analysed separately. We found that the clinical World Health Organization (WHO) Score improved after the first postoperative year by 3.1 points, and that this improvement persisted even after 5 years with +3.2 points compared to the preoperative value. Even after 10 years \((n = 20)\) the average score was found to be lower with – 2.2 points.

Analysis of the individual parameter ‘pain’ of the WHO Score confirmed that 1 year after surgery 22/32 of the long-term observed patients had less pain than prior to the osteotomy, seven remained unaltered and three claimed to be worse off than before. Five years postoperatively 18 had less pain than before surgery, 11 were now unaltered to the preoperative pain status and the remaining three had worsened.

The parameter ‘ROM’ in the long-term patient collective \((n = 32)\) had improved in one patient 11.6 years after surgery, while in 28 ROM remained unchanged to preoperative values and in three the value joint motion had deteriorated. After 1 and 5 years, when compared to the preoperative status, a slight improvement of 0.05 points of the average overall score was calculated.

Genu valgum correction resulted in an average 7° one year after surgery and did not change at the 5-year follow-up. Genu varum were averagely corrected to 3° valgus at the 1-year control and showed a slight loss of correction by 0.5° at the 5-year follow-up, which did not change over the ensuing observation period.

**Complications**

In one case of supracondylar osteotomy a superficial wound infection was observed, needing surgical revision and debridement. The patients treated with a plaster tutor after high tibial osteotomy all needed subsequent intensive physiotherapy to combat the inevitable joint stiffness. In one of these knee joints it was necessary to perform a mobilization under anaesthesia because of persistent stiffness despite physiotherapy. One patient needed joint replacement of both knees, 13 years after initial osteotomy on the left side and 8 years after osteotomy on the right side.

**Discussion**

Haemarthropathies of the knee with marked unicompart-mental changes and correlating axial malalignments can significantly be improved concerning the parameters discomfort and pain over a notable length of time by means of corrective osteotomy. Compared to the ‘normal’ arthrotic joint this phenomenon in the usually more severely damaged haemarthrotic joint may be explained by two mechanisms.

First, by correction of the biomechanical axis, joint congruency is improved and through thinning of the soft-tissue mantle, pressure on the articulating surfaces is decreased \([7]\).
Joint function becomes more harmonious, and excessive unit loads that exceed the tolerance level of normal articular cartilage and subchondral bone are avoided.

The second mechanism deals with the biology of the joint: perception of pain occurs via the joint capsule as well as the intramedullary cavity [8]. Impairment of microcirculation in the venous sinusoids of the marrow cavity with an increase in intraosseous pressure, as observed in osteoarthritis [9], may lead to microarchitectural changes with compression of intraosseous nerve endings, ultimately resulting in severe pain [10]. During osteotomy, the marrow cavity is opened, the venous congestion decreased and, by this, a normal venous drainage achieved. Although joints of haemophilic patients are often considerably more damaged than are the joints of ‘ordinary’ patients suffering from osteoarthritis, the basic mechanism remains much the same.

Although many authors recommend a slight overcorrection when performing supracondylar osteotomies for the ‘normal’ osteoarthritic knee, as protection against postoperative reversionization [11] an overcorrection does not seem advisable for the haemarthrotic knee, as more often than not the contralateral compartment also shows some degree of damage. Mild to moderate degenerative changes to the femoropatellar complex are not considered as contraindications for an osteotomy in the vicinity of the knee [12]. Our results demonstrate that with correction of the axis moderate cartilage degenerations in the femoropatellar complex and in the contralateral compartment can be tolerated.

Particularly in the usually polyarticularly afflicted haemophiliac, the treating surgeon should not only contemplate the results of corrective osteotomy for one specific joint but also needs to assess the effects a change of axis may have on the whole limb. Correction of genu varum will inevitably lead to a compensation in the hip in form of coxa valga. An abduction-contracture of the hip must be treated before a genu valgum is corrected, otherwise a functional leg-length discrepancy and pelvis malalignment may result. The deformity in the ankle joint with typical medial slant of the talus needs either conservative or surgical attention after corrective osteotomy of the knee. On the other hand, an axial correction of the knee with simultaneous treatment of a flexion contracture by means of a supracondylar extension osteotomy or arthroscopic joint débridement can normalize the gait pattern and eliminate the constant flexion position the hip joint was forced to hold [8]. This is just one example of how a neighbouring joint may positively be influenced by an osteotomy in the vicinity of the knee.

The long-term results after corrective osteotomy obtained from patients who were not haemophiliacs show marked discrepancies, with good outcomes varying between 45 and 80% [8]. Good results tend to become increasingly more seldom the longer the postoperative observation period. Furthermore, it must be appreciated that standardized criteria for postoperative assessment do not exist, severely hampering the comparability of various studies. A long-term follow-up after corrective osteotomy in the haemophiliac does not exist to our knowledge. Rodriguez-Merchan and Galindo [13] reported on a middle-range follow-up (6.5 years) with 14 proximal tibial osteotomies for haemophilic arthropathy of the knee, in which 11 patients showed benefit at the time of follow-up.

**Comparison to other studies**

A comparison of our results to those obtained from haemophiliacs initially treated with a total knee arthroplasty (TKA) is difficult, the major problem being that in many studies numbers are small and follow-up is short. Luck and Kasper [14] reported on 20 years of experience with TKA for haemophilic arthropathy incorporating 46 cases. However, a drawback of the review was the use of varying endoprosthetic models, inevitably making numbers smaller and follow-up shorter. In 2002, Silva and Luck [15] presented a retrospective analysis of 90 TKAs. With failure (revision, radiographical loosening or infection) as the endpoint, 10 years survivorship was found to be 74%. The mean follow-up was 7 years.

An excellent review regarding the outcome of TKA in haemophilia is given in the article by Beeton et al. [16]. The authors conclude that arthroplasty, particularly of the hip and knee, can be a valuable option in the management of severe haemophilic arthropathy. It seems important to point out that all studies cited do not provide a follow-up longer than 7 years.

**Summary**

Between 1974 and 1984 we performed 52 corrective osteotomies in the vicinity of the knee on patients suffering from haemophilic arthropathy. Forty-five patients were adequately followed-up at an average 11.6 years postoperatively. Thirty-eight showed an improved clinical score, two had a marginal decrease at the time of follow-up by an average 0.003 points. One patient needed subsequent joint replacement of both knees, on the left side 13 years after osteotomy and on the right side 8 years after osteotomy.

Even in cases of marked joint destruction, corrective osteotomy shows acceptable long-term clinical results, underlining the feasibility of this management option in the treatment of haemophilic arthropathy of the knee. However, this therapy should only be contemplated in those patients where damage is unicompartmental and a corresponding axial deviation is found.

**Conclusions**

The patients we report of here were all primarily treated with a corrective osteotomy because at the time there was no satisfactory
knee joint replacement system available. Surprisingly, the long-term results are so positive that despite good prosthetic systems being readily available, osteotomy should nevertheless be contemplated even nowadays, for unicompartmental haemarthrotic degeneration with correlating axial malalignment. Correction of the axis is a prerequisite to improve the biomechanical situation, yet it is imperative that subsequent intensive muscular training ensues.

Long-term observation of haemophiliacs treated with an artificial knee joint early in life will show whether these patients have an overall higher quality of life. It must be contemplated that a continuous decrease of the afflicted joint's ROM can only marginally be improved by implantation of a prosthetic device. Especially in the younger person, it therefore seems prudent to ascertain the patient's expectations and mutually determine the management option that is most likely to achieve these.

References

Knee joint débridement in haemophilia
H.H. Eickhoff

Introduction

From childhood onwards in patients with severe haemophilia A or B as well as with von Willebrand’s syndrome, spontaneous bleeding into joints without adequate factor substitution leads to inflammatory changes in the synovium. Giving preference to the areola tissue zones of the synovial membrane, it results in villous hyperplasia [1], proliferation of the stroma and perivascular round-cell infiltration [2]. Persisting synovitis and direct damage caused by haemoglobin and its degradation products finally leads to progressive damage of the joint cartilage.

In the lower extremities, the knee joint shows the greatest degree of pathological, clinical and radiological changes. Untreated, it will develop into chronic synovitis and haemophilic arthropathy with severe joint destruction. Over the age of 30 years, 90% of the knee joints are already severely destroyed. Subjectively, patients complain of increasing pain and limitation of movement. The clinical picture shows contractures with reduction in extension and flexion, as well as deformities with a varus or valgus leg axis.

Chronic synovitis and joint destruction are often present simultaneously. The presentation of individual pathological parameters is variable. In synovitis, an active inflammatory haemorrhagic form can be distinguished from a more bland hyperplastic granulomatous form. The degree of severity of the arthropathy can be graded according to various criteria. The classification has been shown by Arnold and Hilgartner [3].

In principle, the arthropathic joints are approachable via conservative and operative measures. Joint débridement (‘cleaning the joint’) is counted as a joint-preserving intervention. It involves the removal of destroyed cartilage fragments, disrupted parts of the meniscus, osteophytes and interfering scarring. The indication for joint débridement is limited to medium to severe arthropathic stages in younger patients. It provides an interim solution before endoprosthetic knee replacement.

In view of the underlying pathology, débridement is usually combined with late synovectomy. In the presence of an axis deformity or contracture, an axis correction or soft-tissue release may be necessary so débridement is just a part of the respective operation. With progression of the joint pathology, the existing clinical and radiological pictures are affected more by arthropathic destruction, which then necessitates extended débridement. The aims of débridement are pain reduction, prevention of recurring irritation and improvement of function.

Débridement can be performed by an open technique, as in late synovectomy with arthrotomy, or by a minimally or less invasive arthroscopic technique. In principle, every operative procedure requires adequate factor substitution. Every surgical procedure in haemophiliacs should be performed only in collaboration with an experienced haematology department. Preoperatively, factor replacement should be administered to produce a concentration of 30–40%. Immediately before surgery, factor activity should be raised to 80–100% by giving approximately 30–40 IU/kg body weight. Up until the fourth postoperative day, the factor concentration should be kept at 60%, and until the 14th day a factor concentration of 50% should be maintained. During the following period of intensive rehabilitation, factor concentration should be kept at 20% [4].

Arthrotomy and débridement

The open procedure requires an extended joint opening with incision of the knee extension apparatus. A midline incision with medial parapatellar entrance and eversion of the patella is recommended. Scar tissue and synovial tissue is excised. Completely destroyed cartilage particles are curetted and the joint surfaces are smoothed. Disruptive osteophytes are trimmed. Free bodies are removed completely. In lateral patella subluxation, a lateral release can be performed without any problems.

Rodriguez-Merchan et al. [5] reported on 11 patients with advanced arthropathy during a mean follow-up period of 4.5 years. The clinical results using the Hospital for Special Surgery (HSS) score were excellent in four, good in five and fair in two cases. The authors recommend that débridement should be considered in the young haemophiliac to avoid or delay total knee arthroplasty. The operation may give the patient years of life without pain and appears to slow the development of radiographical changes.

Soreff [6] reported on three cases with good results in a follow-up period of 1–5 years. Hovy [7] reported on nine knee joints in which an open débridement is combined with
Arthroscopy and débridement

As with the open procedure, débridement is usually combined with a late synovectomy. In the arthroscopic procedure, 4–6 portals are installed through which the optics and the instruments can be introduced. In this way, the soft-tissue trauma, in particular to the extension apparatus, can be minimized. To distend the joint, the author uses non-electrolyte solution with a pressure- and flow-controlled irrigation pump. In severe arthropathy, adhesions, scars and joint contracture are a major problem because of impaired distension of the joint cavity and orientation. The surgeon requires patience and a great deal of experience in arthroscopy. For scar removal and tissue ablation, in addition to a shaver system, electrosurgical instruments, such as the ArthroCare™ device, are strongly recommended.

Eickhoff et al. [4] reported 10 cases of arthroscopic débridement in combination with late synovectomy. The mean follow-up time was 5 years (range 4–6 years). Comparison of preoperative and postoperative pain grading showed significant pain reduction. The extension deficit had a mean preoperative value of 10° (0°–30°) and 5° (0°–10°) at follow-up. Six cases showed an improved, one case a worsened and three cases an unchanged extension deficit.

Eickhoff and Wiedel [8] reported nine cases of late synovectomy and débridement with a 10–15-year follow-up. There was evidence of progression of the arthropathy. The longer the follow-up, the greater the changes, which were demonstrated in all the knees. Some of the knees did not change stage according to the Arnold and Hilgartner scale, but there were progressive bony changes (Table 17.2).

Conclusions

Even in the age of increasing endoprosthetic possibilities, joint débridement in haemophilic knees has its place as before and should, with the appropriate indications, usually be performed with a late synovectomy. Joint débridement can be performed just as satisfactorily in open as in arthroscopic procedures with good mid-term results in haemophilic knees. The arthroscopic operation, more so than arthrotomy, is a demanding procedure and the surgeon should be skilled in the technique.

The indications are young patients, with moderate to severe arthropathy, in whom conservative therapy is no longer adequate and implantation of a knee endoprosthesis is not yet necessary. With this in mind, débridement should at least stand the chance to obtain a good mid-term result. With poor preoperative joint function, especially with a significant pre-existing extension deficit, the expected result is much worse, so that the indication for an operation should not be delayed too long. In particular, progressive arthrofibrosis and secondary muscular atrophy are responsible for a worse prognosis.

Even when débridement fails, a follow-up procedure with endoprosthesis can be carried out relatively easily. Because of this, and as a result of the reduced soft-tissue damage, the author prefers the arthroscopic route for the first operation. In the most severe stage V arthropathy, with considerable contractures or obvious axis deformities (> 15° valgus > 5° varus), débridement is no longer indicated. With the rising probability of expected failure of a joint-preserving operation, the modern knee endoprosthesis with modular components should be given preference. Even in view of the increased costs of an operation, a definitive solution should be provided for hopeless cases.

Table 17.1 Results of open synovectomy and débridement (n = 4). (Modified from [7].)

<table>
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<th>Stage Preop</th>
<th>Extension lag (°) Preop</th>
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Table 17.2 Results of arthroscopic synovectomy and débridement (n = 9). (Modified from [8].)

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References

CHAPTER 18
Flexion contractures of the knee in haemophilia

M. Silva and J.V. Luck Jr

Introduction

Contractures, defined as the lack of full passive range of motion resulting from joint, muscle or soft-tissue limitation [1], are a usual component of haemophilic arthropathy. These contractures are the result of a combination of recurrent haemarthroses causing fibroblastic proliferation and progressive arthropathy and extra-articular intramuscular bleeding episodes leading to fibrosis [2].

The prevalence of joint contractures in severe haemophiliacs has been reported to be between 50 and 95% [2]. Rizza [3], studying 43 severe haemophiliacs under 20 years of age, found that 44% of them had contractures of greater than 10°. The knee, the most commonly involved joint in haemophilia and certainly the one most responsible for pain and disability, is also the one that has been more frequently associated with fixed flexion contractures as well as loss of flexion range [2,4].

Pathophysiology

The single most important factor in the pathogenesis of a knee contracture in a haemophilic patient is the presence of joint bleeding [2,5,6]. In its acute stage, a single haemarthrosis will result in an increase of the intra-articular fluid volume, with a concomitant increased intra-articular pressure and distention of the joint capsule [5]. Joint distention causes reflex muscle inhibition of the quadriceps, mediated through activity of intra-capsular receptors [7]. A flexed position is adopted by the knee not only as a result of the muscular imbalance [8] but also as a simple reflex response to minimize the resultant intra-articular pressure [5]. Experimental capsular distention by intra-articular plasma injection demonstrated that the minimum pressure is obtained with the knee flexed between 30° and 45° [9]. If treatment is started soon after the initiation of an acute haemarthrosis, and the response is adequate, the knee will probably regain full extension.

However, a recurrent haemarthrosis, untreated or unresponsive to medical treatment, may result in a fixed flexion deformity. Once in a stage of recurrent haemarthrosis, blood breakdown products overwhelm the ability of the synovial membrane to take them in by phagocytosis. As a result, the synovium becomes thicker and hypervascular [10]. This factor will further increase the already elevated intra-articular pressure, forcing the knee to a constantly flexed position. With the knee held in flexion, the knee flexors overcome the weakened knee extensors, pulling the tibia into posterior subluxation on the femoral condyles [6]. This progressive posterior traction causes a shortening and tightening of the posterior knee capsule [11]. The atrophy of the vastus medialis often results in lateral subluxation of the patella. In addition, contracture of the iliotibial band draws the tibia into external rotation on the femur.

The thickened hypervascular synovium becomes easily entrapped within the joint, resulting in new bleeding episodes. Chondral erosions develop as a result of degradation mediated by enzymes released by the disrupted synovial cells [12–16] as well as direct synovial invasion of articular cartilage [17]. In addition, there is experimental evidence that haemarthrosis blood has an inhibitory effect on proteoglycan synthesis and matrix dissolution [13,18]. Severe muscular atrophy and joint subluxation progress with the arthropathy. Extensive joint surface erosions will lead to end-stage arthropathy, which is almost always complicated by severe contractures secondary to arthrofibrosis as the hypertrophic synovium is replaced by dense fibrous scar [17].

Prevention

Preventive measures should be directed at reducing the number and severity of haemarthroses by adequate medical surgical treatment. Haemarthrosis in a haemophilic joint without arthropathy should be managed very aggressively, including regular factor replacement, restorative physical therapy and close clinical follow-up. Administration of clotting factor concentrate should be started immediately following the onset of the bleeding episode and continued until the joint has returned to normal [19]. The goal here is to decrease the intra-articular volume, allowing the joint to return to its normal extended position, and prevent further articular damage. Short-term immobilization (for up to 2 weeks), aimed to accelerate the haematoma resorption and relieve the pain of muscle spasm,
has been proved effective in preventing contractures [2,20]. Physical therapy, especially strengthening, plays an important part in the prevention of joint contractures. Regimented strengthening programmes also appear to reduce the incidence of bleeding episodes [21,22].

Management of the established knee contracture

If initial efforts to prevent the development of knee contractures have failed, attempts at correction should be made as soon as possible. Available treatments fall into three categories: physiotherapy and rehabilitation, orthotics and surgery.

Physiotherapy and rehabilitation

The role of physiotherapy in the case of an established knee contracture is limited. The main purposes of rehabilitation are to obtain pain relief, increase range of motion and muscle strength, improve posture and maximize function [2,23–25]. A careful planning of the rehabilitation programme should include the analysis of the impairments, disabilities and handicaps present at the time of treatment [6,25–28]. This approach was introduced by the World Health Organization’s International Classification of Impairments, Disabilities and Handicaps (ICIDH), defining impairments as any loss or abnormality of physiological or anatomical structure of function, disabilities as any restriction or lack of ability to perform an activity in a normal manner, and handicaps as a disadvantage resulting from an impairment or disability [26,27].

The haemophilic patient with arthropathy is impaired by pain, limited motion, muscle weakness with atrophy, and joint subluxation, as well as the ever-present fear of haemarthrosis [6,28]. The presence of pain limits the patient’s ability to perform active exercises to regain range of motion and muscle strength. As a result, the physiotherapy should be initially focused on pain relief [6]. Several methods for pain relief have been described, including but not limited to manual therapy with joint mobilization, cold therapy, ultrasound, transcutaneous nerve stimulation and hydrotherapy [6,20,23,24]. Muscle stretching and strengthening should be started as soon as possible, including not only the quadriceps but also the hamstrings, the hip abductors and extensors and the calf muscles for involvement of the lower extremity [6].

Once the knee is less painful and the range of motion is restored to its maximum, assessment of the established disability can be performed. A slight lack of knee extension is usually compensated by hip flexion and equinus foot position, allowing the patient to stand and walk with a balanced centre of gravity. If this is the case, a postural gait and functional training are needed in order to reduce the impact of the disabling condition. However, if the articular contracture is severe, leading to major disabilities and handicaps, additional treatment, either with orthoses or surgery, will be required.

Orthotic and corrective devices

Several specific devices have been utilized in haemophilic patients for the correction of knee flexion deformity, including serial casting, extension–desubluxation orthoses (EDO), reversed dynamic slings and inflatable splints. However, there is little information available on the results of the use of these devices. Early reports indicated the benefits of their use, but there are very few recent reports on these methodologies. This is probably because, with the advent of clotting factor replacement and prophylaxis, the incidence of severe knee flexion deformity in developed countries has been significantly reduced.

Serial casting, with posterior wedges, has been used with relative success. The recommended regimen includes the use of a cylinder cast with a posteriorly based wedge, made at the level of the knee joint, which is opened by approximately 10° every 2–3 days. The cast should be well padded at points of corrective force and changed every week to avoid pressure sores over the patella, anterior thigh or Achilles tendon. In 58 cases treated by Fernandez-Palazzi and Battistella [5] with this technique, an average correction of 33° was obtained. However, it has to be recognized that this is a time-consuming procedure which carries additional risks, such as skin necrosis and joint subluxation [5,29].

The use of reverse dynamic slings for the treatment of haemophilic knee flexion deformity was described by Stein and Dickson [29] in an effort to overcome the limitations of serial casting. It was proposed that a combination of forces, pushing the thigh down against upward counterpressure of the slings under the calf while the knee was actively flexed, gradually corrected the flexion deformity [29] (Fig. 18.1). In their original report, they described the use of reverse dynamic slings in 10 patients (average flexion contracture of 38°). Results were compared to those obtained in eight patients (average flexion contracture of 25°) treated by serial casting. There was a significant reduction of the flexion contracture in both groups, but the reduction was significantly higher in the group with reverse dynamic slings (34° vs. 9° in the group with serial casting).

Fig. 18.1 Diagram of a reverse dynamic traction system. Longitudinal skin traction is applied to the lower limb (A). A reversed sling applied over the distal aspect of the femur is held tense by weight on cord B, driving the knee into extension.
Moreover, the group treated with reverse dynamic slings required less time to achieve this result [29]. No complications were seen in the group treated with reverse dynamic slings, but one of the patients treated with serial casting developed recurrent haemarthrosis.

Results of the use of a modified system of reverse dynamic slings in 10 patients with severe flexion deformity (> 30°) were published by Kale et al. [30]. The mean duration of the deformity was 10 months. From a mean flexion contracture of 45°, it was improved to a mean contracture of 7° after 6–8 weeks of treatment. The authors concluded that the dual-force system offers an effective means of correcting knee flexion deformity [30]. However, it has to be recognized that hospitalization and close supervision are required to achieve satisfactory results with dual-force systems. Inflatable splints around the knee, a system that is suitable for home use, have been utilized for the treatment of haemophilic knee flexion deformity with satisfactory results [4,31].

In order to allow simultaneous extension and desubluxation of the contracted knee, a Quengel cast was adapted by adding small metal hinges between the upper and lower portions of the long-leg cast. These extension–desubluxation hinges (EDH) were described initially by Jordan [32] and were later modified by Wallace at Orthopaedic Hospital, Los Angeles [33]. The hinges, with adjustment screws for extension and desubluxation, are placed medially and laterally to the knee with the axes of the hinge aligned with the centre of rotation of the knee (Figs. 18.2 and 18.3). They are indicated for knee flexion contractures of relatively recent onset without severe arthropathy. Constant corrective forces are applied gradually by the patient, on a daily basis, for approximately 3–4 weeks. Once the flexion deformity is less than 10–20°, a cylinder plaster cast should replace the hinged cast. These last few degrees may be further corrected by wedging the cylinder. EDH casts were extensively used at the authors’ institution during the 1960s and 1970s because severe knee flexion contractures were commonly seen at that time. Nowadays, severe flexion contractures of the knee are very infrequent in the authors’ institution and EDH casts are no longer used. However, in developing countries, where access to clotting factor is limited and severe knee flexion contractures are still seen, the use of EDH casts has provided an alternative treatment, especially for young patients with early stages of arthropathy [25].

Surgery

The types of surgical procedures that can be performed to correct a haemophilic knee flexion deformity fall into two categories: corrective surgery (soft-tissue release and osteotomy), and reconstructive surgery (total knee arthroplasty).

Corrective surgery

Soft-tissue procedures, including hamstring and posterior capsule releases have been recommended for the treatment of fixed knee flexion contractures in haemophiliacs [34–36]. Rodriguez-Merchan et al. [34] reported results of 16 hamstring tenotomies and posterior capsulotomies in 10 haemophilic patients with severe knee flexion contractures (30–45°). The average age of the patients was 17 years (range 16–24 years) and the average follow-up was 9.5 years (range 6–13 years). A very strict physical therapy programme was required for as long as 6 months postoperatively. An average decrease of 25° in the amount of flexion deformity was obtained. In all 16 knees, radiographical progression of the arthropathy was observed [34].

Wallny et al. [35] reported results of hamstring release and posterior capsulotomy on 19 haemophilic patients with knee flexion contractures. The mean follow-up was 12.5 years (range 15–20 years). Although an immediate postoperative full extension was achieved in 16 cases, the range of motion decreased over time. According to the authors, over the course
Fig. 18.3 (a) Photograph of a 6-year-old haemophilic patient with a fixed flexion deformity of his left knee. The knee had a fixed flexion contracture of 60°. An associated pelvic tilt to the side of the knee flexion deformity, hip flexion and equinus foot position was observed. (b) Extension–desubluxation hinges (EDH) were used. The EDH were adjusted on a daily basis for approximately 4 weeks.

of the study eight cases demonstrated a recurrent knee flexion contracture that was the same or even worse than before the operation. However, numbers for the average range of motion and the average flexion contracture present at the time of the latest follow-up were not provided. Although initially beneficial, soft-tissue procedures for correction of severe fixed knee flexion contractures are often insufficient to maintain full correction [36]. Soft-tissue releases may have a place for a severe contracture in a very young patient with early stages of arthropathy. Night splints in full extension may help maintain the correction.

Caviglia et al. [37] reported on the use of extensor supracondylar femoral osteotomies for the treatment of long-standing flexion deformities in 19 haemophilic patients. Although all patients succeeded in walking after the intervention, there was a very limited increase in range of motion in only three patients. Furthermore, instead of correcting the original deformity, a secondary deformity was created above it with the alteration in joint-loading forces.

Reconstructive surgery

In patients with advanced arthropathy, knee flexion deformity may be corrected at the time of total knee arthroplasty (TKA), which is the authors’ preference. The main indication for a TKA in a haemophilic patient is incapacitating pain that is unresponsive to medical treatment. Contractures, especially in severe flexion, and limitation in range of motion are contributing factors.

Advanced arthropathy of the knee is often associated with severe arthrofibrosis and marked muscle atrophy of the quadriceps. A careful evaluation of bony deficiencies, as well as subluxation and angular deformity, is essential in preoperative planning. The tibia subluxes laterally and posteriorly on the femur and goes into external rotation. This may draw the patella over the lateral femoral condyle, or even result in frank lateral dislocation, often eroding the patella to a very thin wafer with inadequate bone stock to secure a patellar component. Marked deepening of the trochlear groove opposite the patella...
is quite common. The epiphyses are oversized as a result of hyperaemia from haemophilic synovitis, whereas the diaphyses are often narrower than normal for the patient's size. The normal posterior tilt of the tibia is often absent or reversed as a result of ambulation with a flexion contracture during growth.

A standard medial parapatellar approach, under tourniquet, is used. Completing the knee replacement within a single tourniquet time is frequently but not always possible because of the complexity of exposure and bone reconstruction. Surgical exposure of severe contracted knees is challenging, and more time-consuming than usual. With severe arthrofibrosis, extensive releases, as well as débridement, are necessary in order to evert the patella and to obtain adequate flexion to prepare the distal femur. In severe cases of fibrous ankylosis, making the tibial cut first can greatly facilitate exposure. However, this must be done very cautiously in order to avoid damage to popliteal neurovascular structures which may be adherent to the posterior capsule. Resection of the shortened posterior cruciate ligament and popliteus tendon is usually necessary, especially in severe contracted knees. The suprapatellar fat covering the distal femur, if still present, should be preserved, as it is a barrier to quadriceps adhesion. In patients where the suprapatellar fat has been replaced by fibrous tissue, restoration of motion is especially challenging.

Patients going to surgery with very limited flexion may require quadricepsplasty as part of the surgical exposure. Quadricepsplasty is often associated with an extensor lag of 6 months or longer. It is important not to overlengthen the extensor mechanism in order to avoid a permanent extensor lag. Our preferred method, whenever possible, is to release tight fibres of the quadriceps tendon to allow 70–80° flexion rather than perform a 'V-Y' lengthening.

A thorough resection of osteophytes, especially in the posterior aspect of the knee, is necessary to reduce the flexion contracture. It is especially important not to put the components in so tightly that it is difficult to get full extension. If at trial reduction some flexion contracture remains, the posterior capsule should be released from the distal femur under direct vision. It
is recommended that the surgeon’s non-dominant hand pushes the capsule away from the femur to protect the popliteal neurovascular structures. For patients with small flexion contractures, the combination of resection of osteophytes, elevation of the posterior capsule and the use of adequately sized components should be enough to correct the deformity. In patients with severe flexion contractures, however, resection of additional bone from the distal femur is likely to be required [36,38]. Special care must be taken in order to leave enough bone to still allow appropriate tracking of the patella and not result in ‘patella baja’. If, even after additional bone has been resected, it is still not possible to correct the flexion contracture, the proximal heads of the gastrocnemius complex on the femur can also be released [38]. Once adequate knee extension has been obtained, the anterior medial capsule should be closed, with the knee in about 50° of flexion. A knee immobilizer is generally used for 1–2 days after surgery.

Aggressive physical therapy and a high level of patient co-operation are essential to keep the gained knee extension and improve the total arc of motion. Continuous passive motion may be useful part-time during the day, especially on the first postoperative days. Physical therapy should be started the day after surgery, being performed twice daily while in the hospital and 5 days a week for first 2–3 weeks after leaving the hospital; thereafter 3 days a week usually for a period of 6–9 weeks.

If necessary, knee manipulation should be performed between day 7 and 10, after the wound has begun to consolidate and before significant adhesions have formed. At the time of manipulation, it is important to balance forces about the knee to avoid bending forces about the distal femur and proximal tibia that might result in pathological fracture as juxta-articular osteopenia is present in most of these patients.

A total of 106 TKAs in haemophilic patients have been performed at the authors’ institution between 1975 and 2001. A recent review was performed in 93 TKAs that have been followed for more than 1 year. An average preoperative knee flexion contracture of 19° (range 0–50°) was recorded. The flexion deformity measured immediately postoperatively was smaller in 71% of the cases by an average of 15.5° (range 2–35°), the same in 9% of the cases, and greater in 20% of the cases by an average of 7° (range -15° to 1°). At the latest follow-up (mean 7.4 years; range 1–25 years), an average knee flexion deformity of 9° was recorded. Similar results were described by Lachiewicz et al. [39], reporting an average reduction in flexion contracture of 14.5° (range -5° to 45°) after the TKA with a remaining 6° of flexion deformity in 11 of 24 cases, and by Teigland et al. [40] who reported an average correction of 23° of the flexion contracture after the TKA.

Conclusions

The knee is the joint most frequently affected by flexion contractures in haemophiliacs. Early haemarthroses, the single most important factor in the pathogenesis of a knee contracture in a haemophilic patient, should be managed aggressively with aspiration, clotting factor concentrate and restorative physical therapy. If efforts to prevent the development of knee contractures fail, attempts at correction should be made as soon as possible. Serial casting and corrective orthoses can be used for the treatment of knee flexion contractures in the presence of a relatively normal joint. However, their indication is limited when access to clotting factor is available and other options can be utilized. Soft-tissue releases and osteotomies, although sometimes beneficial, are often insufficient to gain full correction of a severe flexion contracture. In the presence of advanced haemophilic arthropathy, total knee arthroplasty, with attempt at correction of the flexion contracture, is the treatment of choice.

References

References:


CHAPTER 19

Flexion contracture of the ankle in haemophilia

A. Llinas

Introduction

Plantar flexion contracture of the ankle is a common finding among haemophiliacs. It is a disabling condition because it affects posture, gait and the load distribution of the foot. It is likely that other elements coexist with the abnormal kinetics and kinematics; for example, muscle weakness, poor muscle control and abnormal cocontraction [1]. A rapid resolution of this condition is imperative to avoid bleeding from neighbouring joints, which are affected by the unnatural physiological loading conditions brought about by the equinus deformity [2] (Fig. 19.1).

The alteration in posture results from the need to compensate for the posterior displacement of the centre of gravity originated by the plantar flexion of the ankle. The patient must allow the knee and the hip to go into flexion, and the lumbar spine to increase its lordosis. The exact amount of flexion of the knee and hip, as well as the magnitude of the lordosis required, is proportional to the degree of fixed plantar flexion of the ankle.

The alteration in gait is characterized by forefoot strike to initialize the cycle and premature plantar flexion in early to mid stance [3,4]. Equinus gait is associated with increased stance-phase knee flexion or crouch [5]. The objective of treatment is to produce greater ankle dorsiflexion during stance and swing as well as decreased knee flexion at foot contact.

The alteration in the load distribution of the foot results from the inability of the patient to place it in a plantigrade position. Pedobarographical data indicates that most of the load is borne by the metatarsals heads and the toes. The metatarsophalangeal joints will function in a dorsiflexed position, adding another component to the deformity of the lower extremity [6] (Fig. 19.1).

Classification

The clinical appearance of the patient with a plantar flexion deformity of the ankle is similar in all cases; however, the source of the problem may be at different levels of the extremity. In order to underscore the need to address the plantar flexion deformity of the ankle at the right level or levels of the extremity, we have developed the following aetiological classification.

Type 1 Chronic synovitis of the ankle
Type 2 Anterior tibial osteophyte
Type 3 Arthrosis of the ankle
Type 4 Contracture of the muscles from the superficial posterior and/or deep posterior compartments of the leg

A variety of resources and procedures will be required to solve the various origins of this deformity, which spans the anterior aspect of the ankle to the proximal and posterior aspect of the knee [7].

Treatment

Type 1: chronic synovitis of the ankle

The severe pain and joint swelling experienced with acute intra-articular haemorrhage of the ankle will drive the ankle...
initially into plantar flexion. Repetitive bleeding when treatment is inappropriate, or when inhibitors develop, will result in synovial hypertrophy. The patient will soon learn that active or passive dorsiflexion will produce synovial impingement and, consequently, a new bleed. What started as an antalgic plantar flexion attitude of the ankle will evolve into a structured protective plantar flexion deformity, because of retraction of the posterior ankle capsule and shortening of the Achilles tendon.

Treatment should be orientated towards the interruption of the vicious cycle of bleed–synovitis–bleed, by means of appropriate factor concentrate replacement and/or synovectomy. The efforts to stop articular bleeds should be complemented by a physiotherapy programme orientated toward the recuperation of dorsiflexion and proprioception of the foot and ankle [5]. From the standpoint of range of motion, encouraging initial dorsiflexion of the ankle may be achieved when working with the knee in deep flexion. The focus of the physiotherapy effort should be on elongating the posterior ankle capsule and the retraction of the Achilles tendon. Orthotic devices, some of which may provide dynamic dorsiflexion, may be of help in achieving this goal [8–10].

Type 2: anterior tibial osteophyte

A radiographical finding that is characteristic of haemophilic arthropathy is the presence of a marginal osteophyte on the anterior portion of the tibia in the ankle [11] (Fig. 19.2). This osteophyte may be associated with chronic active synovitis, or be a vestige of previous articular inflammation that has subsided. The prominence of the osteophyte produces impingement of the synovium during dorsiflexion of the ankle [12]. The pain generated by this phenomenon prevents the patient from challenging the osteophyte and the latter will continue to grow, producing greater plantar flexion deformity of the ankle.

The presence of the osteophyte constitutes a mechanical impediment to dorsiflexion, therefore the treatment of this condition calls for the removal of the osteophyte, by arthroscopy or open arthrotomy. This limited procedure, often referred to as cheilectomy, requires that the articular cartilage be in good condition for the results of the procedure to be optimal (Fig. 19.2). As with plantar flexion deformities caused by chronic synovitis, the focus of the physiotherapy effort in this condition should be on elongating the posterior ankle capsule and the retraction of the Achilles tendon.

Type 3: arthrosis of the ankle

Chronic pain and joint deformity in terminal haemophilic arthropathy may also result in a plantar flexion deformity. The deformity typically results from a combination of the contracture of the posterior capsule of the ankle, retraction of the Achilles tendon and collapse of the dome of the talus as a result of osteonecrosis and wear [13]. Ribbans developed a combined clinical and radiographical scoring system specifically for haemophilic ankle arthropathy, which is helpful in defining treatment [2]. This scoring system demonstrated less interobserver variability than that of Pettersson and Nilsson [14], or that of Gamble et al.’s [15] modification of the Mazur et al. [16] scoring system.

Severe arthropathy of the ankle with plantar flexion deformity and intractable pain should be addressed with a tibiotalar fusion. Arthrodesis of the ankle is the subject of Chapter 23 so we will not expound on the subject at this point. However, we would like to highlight that intrinsic to this surgery in the patient with a severe flexion contracture of the ankle, is a high degree of technical difficulty encountered in bringing the foot to a neutral position. The contracture of the posterior capsule of the tibiotalar joint as well as that of the subtalar joint and the retraction of the Achilles tendon may impede dorsiflexion of the foot even after sufficient bone has been removed from the tibiotalar joint for the purpose of the fusion. A varus deformity of the hind foot may be associated with ankle arthrosis, when the original lesion involved the muscles of the deep posterior compartment of the calf. This deformity may also prove to be difficult to correct. The surgeon should be prepared to approach the ankle posteriorly, in order to perform capsulotomies and, less often, Achilles tendon lengthening.
Type 4: contracture of the muscles from the superficial posterior and/or deep posterior compartments of the leg

In traumatic events of the leg in non-haemophiliacs, a primary consideration in the emergency room is to rule out a compartment syndrome. However, in haemophiliacs, perhaps because the level of energy that produces a bleed is often low, and also, because patients are seen by health-care workers who are not familiar with high-energy trauma, compartment syndromes are often overlooked [17,18]. Prolonged increased compartmental pressure will lead to ischaemia within the compartments of the leg, myositis and nerve damage. When the compartment syndrome occurs in an isolated manner, within the superficial posterior compartment of the leg, the gastrocnemius and soleus muscles are injured, leading to muscle scarring, contracture, paresis and, finally, to a plantar flexion deformity of the ankle.

Treatment of the contracture of the gastrosoleus unit requires lengthening of the Achilles tendon and often posterior capsulotomy of the tibiotalar joint and of the subtalar joint. If the patient has a structured flexion contracture of the knee caused by the retraction of the gastrocnemius, a posterior release of the knee will be required simultaneously.

To prevent recurrence of the plantar flexion deformity, a cast with the ankle in the neutral position will be required for 4 weeks, followed by physical therapy [19]. The degree of success obtained by this procedure will be determined by the severity of the lesion created in the first place by the compartment syndrome; that is, by the amount of fibrosis of the muscles and neuropathy. Consequently, considerable difficulties should be anticipated during rehabilitation, and suboptimal results in terms of muscular contraction and force should be expected and discussed with the patient and family prior to surgery.

Conclusions

Plantar flexion deformity of the ankle results from acute or chronic bleeds within the ankle or acute bleeds within the superficial and/or deep posterior muscle compartments of the calf. Initial prevention and treatment of the injuries that lead to plantar flexion deformity of the ankle require measures that are simple and inexpensive when compared to the complexity and cost of reconstructive procedures. The main principle underlying the treatment of haemophilic contracture is the restoration of the patient’s lifestyle and mobility, rather than anatomical or radiographical normality [20].

References

Severe haemophilic arthropathy
Total hip replacement in the haemophilic patient

E.C. Rodriguez-Merchan, J.A. Riera and J.D. Wiedel

Introduction

The first important series of total hip replacements (THRs) in haemophiliacs was published by Luck and Kasper in 1989 [1]. They reported 13 hip arthroplasties; eight patients had required revision, and one required an excision arthroplasty for a Pseudomonas aeruginosa infection. The long-term experience of Luck and Kasper with various types of hip prostheses can be rated as only fair, with a revision rate of about 60% over 20 years. However, the clinical status of all patients was quite satisfactory in that all were free from hip pain and were capable of unlimited unassisted community ambulation. They were substantially better than they had been prior to their initial hip surgery. End-stage hip disease in haemophilic patients poses an unsolved problem. Primary cemented prostheses have a 33% aseptic failure rate 5-14 years after operation, which is higher than would be expected in a comparable group of patients with another form of polyarthritis. One reason for the loosening of cemented hip prostheses in haemophilic patients may be the increased stresses of a stiff-legged gait.

Review of the literature

In 1992, Nelson et al. [2] reported on 39 total hip arthroplasties performed in 38 patients for haemophilic arthropathy. The median age of the patients at operation was 48 years. In 21 patients, 22 hip replacements were reviewed clinically and radiographically, with a median follow-up of 7.6 years. Five of the 22 hips had been revised and three were likely to require revision in the near future. The incidence of revision was compared to other studies of total hip arthroplasty in young patients and the influence of the human immunodeficiency virus (HIV) infection was examined. Total hip arthroplasty was believed to be an appropriate operation for disabling haemophilic arthropathy.

In 1996, Löfqvist et al. [3] reported 13 THRs were performed in 11 haemophilic patients with a mean age of 46 years. According to these authors, the indication for surgery was disabling pain because of advanced haemophilic arthropathy. The surgical technique was the same as for other patients; cemented Charnley prostheses were inserted, using the transtrochanteric approach. The mean duration of follow-up was 7 years. Five hips became loose within 6 years, and a further one after 13 years. Four hips were revised, two of them as a result of infection in patients who were also seropositive for HIV. At the latest follow-up, 10 patients were alive, six had no hip pain and seven could walk a distance of at least 1000 m. Although these results were inferior to those obtained in arthritis, THR should be considered in patients with haemophilia. Löfqvist et al. concluded that this group of patients can expect a fairly high frequency of aseptic loosening after THR. HIV-positive patients also seem to have an increased infection rate. However, according to their findings, they concluded that THR is of value in some haemophilic individuals.

As haemophilic arthropathy infrequently affects the hip joint, Kelley et al. [4] performed a multicentre retrospective study to determine the results of hip arthroplasty in haemophilic patients. Thirty-four hip arthroplasties were performed in 27 male patients at four major haemophilia centres. Twenty-six patients had classic haemophilia and one had factor IX deficiency. The mean age of the patients at the time of the operation was 38 years (range 15-73 years). The mean duration of follow-up was 8 years, with a minimum of 2 years for all patients who were still alive at the time of this review. Four patients were seropositive for HIV at the time of the operation, and 16 patients were seropositive at the time of the most recent follow-up examination. Nine patients (33%) died before the time of this review; seven had been seropositive for HIV. There were 26 total hip arthroplasties performed with cement, six total hip arthroplasties performed without cement, one total hip arthroplasty in which the femoral component was inserted with cement and the acetabular component was inserted without it (so-called hybrid arthroplasty) and one bipolar arthroplasty performed with cement. There were no early infections after these 34 primary arthroplasties. There were three late infections around prostheses inserted with cement, and all led to a resection arthroplasty. Six (21%) of the 28 cemented femoral components and six (23%) of the 26 cemented acetabular components were revised because of aseptic loosening.
The Haemophilic Joints: New Perspectives

Heeg et al. [5] evaluated the long-term results of three total hip and nine total knee arthroplasties in nine haemophilic patients with disabling pain and end-stage arthropathy. These patients have been followed over a period of 2–12 years (mean 6.9 years). One patient had a postoperative haematoma, which was evacuated; two patients required manipulation of the knee because of a limited range of motion. There were no infections. At follow-up, all but two patients were completely free of pain and two patients had occasional pain. The functional improvement was impressive, with an average increase in the knee score from 37 to 80 points postoperatively. The hip score increased from 36 to 85 points. The range of motion was increased in seven joints, unchanged in two joints and decreased in three. One total hip arthroplasty was revised after 9 years for aseptic loosening. One total knee demonstrated non-progressive radiographical evidence of aseptic loosening. Median consumption of coagulation factor concentrate in severe haemophiliacs decreased from 4700 IU/year (range 16 000–144 000) before surgery, to 25 000 IU/year (range 18 000–132 000) at 2 years after surgery. The authors concluded that hip and knee arthroplasty is a valuable option in symptomatic haemophilic patients with disabling arthropathy, in order to obtain pain relief and functional improvement. It is associated with a low rate of complications and may reduce the need for substitution of factor VIII and factor IX.

Takedani et al. [6] evaluated the medium-term follow-up results, effectiveness and suitability of arthroplasty for haemophilic arthropathy. They performed 26 total knee and nine total hip arthroplasty operations on haemophilic patients under appropriate haemostatic management. Postoperative treatment for haemophilic arthropathy is the same as that for osteoarthritis and rheumatoid arthritis. After their operations, patients experienced relief from pain and intra-articular bleeding in affected joints but only marginal improvement in the range of motion. In general, total joint arthroplasty is not indicated for young patients. However, arthropathy can have a severe impact on the active life of patients during their youth. For severe haemophilic arthritis, total knee and hip arthroplasty can lead to a pain-free and improved quality of life. We believe that total knee and hip arthroplasty is a good solution for haemophilic arthropathy before severe deformity occurs.

Beeton et al. [7] reported that in severely affected haemophilic patients arthropathy is a common problem which can lead to considerable pain and functional deficit. Surgical management, including total joint arthroplasty, can be undertaken if conservative management fails. A search of the literature showed that a number of studies describing the use of THR in haemophilia have been published. This paper reviewed the functional outcome of arthroplasty in the different joints, the postoperative and long-term complications, and the impact of HIV. Although complications were commonly described and the surgery was technically demanding, the results suggested that hip arthroplasty can be a valuable option in the management of severe haemophilic arthropathy.

Total hip replacement in the HIV-positive haemophilic

Between 33 and 92% of patients with haemophilia A, and between 14 and 52% of persons with haemophilia B, carry the HIV antibody. In two studies of hip replacement for haemophilic arthropathy with more than 20 patients and more than 3 years’ follow-up, approximately 50% of the patients were known to be seropositive for HIV, contributing to an overall mortality rate at median 7-year follow-up of 20–33% [2,4]. Patients with CD4 levels of > 500 cells/mm³, a positive reaction with anergy testing to intradermal skin antigens, platelet count > 60 000, total leucocyte count > 1000, serum albumin > 25 g/L and no history of opportunistic infections of neoplasm have a postoperative complication risk similar to the general population.

Joint replacement in HIV-positive patients remains uncommon, with most experience gained in patients with haemophilia. Hicks et al. [8] analysed retrospectively the outcome of 102 replacement arthroplasties in 73 HIV-positive patients from eight specialist haemophilia centres. Of these, 91 were primary procedures. The mean age of patients at surgery was 39 years, and the median follow-up was for 5 years. There were 27 replacements of the hip, 74 of the knee and one of the elbow. For 53 arthroplasties the patients had been diagnosed as HIV-positive before surgery, and in 37 the diagnosis had been made after the operation. Analysis of the overall survival of patients in which diagnosis of HIV infection had been made before the operation showed survival of 55% at 10 years after the operation.

The overall rate of deep sepsis was 18.7% for primary procedures and 36.3% for revisions. This is a much higher rate of infection than that seen in a normal population. A total of 44% of infections resolved fully after medical and/or surgical treatment. Analysis of the sepsis-free survival rate of prostheses implanted in primary procedures showed survival rates of 71.8% at 10 years and 54.9% at 20 years. After arthroplasty in the normal population, rates of infection of up to 1.5% are currently considered to be acceptable. From analysis of reports of 715 arthroplasties in haemophilic patients Hicks et al. calculated an overall rate of deep infection of 7.2%, regardless of the HIV status. When patients were known to be HIV-positive, Hicks et al. found an overall rate of infection of 11.7%, compared with 18.7% in our study. In their study patients with low CD4 counts before surgery were more likely to develop deep sepsis.

Total hip replacement for ankylosed hips

Conversion of an ankylosed hip to a THR may be technically difficult because of major local distortions. The simple wish to recover a mobile hip rarely leads to this procedure for a fused hip. It is more often motivated by its painful consequences on
the lower back and ipsilateral knee. To achieve a mobile and stable hip, two factors are essential: the hip abductor muscles must be in fair condition and the restoration of hip biomechanics must be anatomical, with a proper abductor level arm ratio and correction of limb length discrepancy [9]. This conversion frequently leads to a pain-free and mobile hip, but normal gait and walking ability are less often achieved. However, even if there is a persistent limp, requiring a cane for distance walking, the patient always enjoys relief of pain from the back and knee, and being able to sit comfortably.

A cemented Charnley total hip prosthesis was implanted by Rodriguez-Merchan et al. [10] in a 48-year-old man with mild haemophilia (factor VIII 4 IU/dL) in his right spontaneously ankylosed hip. At the time of surgery he was HCV (hepatitis C virus) positive, HIV negative and no circulating inhibitors were encountered. The indication for surgery was long-lasting intractable low back and ipsilateral knee pain. At 2-year follow-up, relief of pain was achieved as well as correction of limb-length discrepancy, with a good result according to the Mayo Clinic hip score. Doses of 50 IU/kg body weight of recombinant factor VIII (Recombinate; Baxter, Glendale, California, USA) were used during the 2 weeks of hospitalization. The dosage was adjusted according to the recovery of factor VIII, with an overall factor consumption of 68 000 IU. As far as we know, this is the first case reported in the literature of a person with haemophilia in whom a spontaneous hip ankylosis has been satisfactorily converted to a total hip arthroplasty with a short-term follow-up. However, much longer follow-up is still needed to ascertain the efficacy of this surgical procedure in haemophilia.

**Total hip replacement in haemophilia patients with inhibitors**

A review of the literature on inhibitors has shown that, with the availability of FEIBA® and activated recombinant factor VII (rFVIIa), haemophilic patients with high-titre inhibitors requiring elective orthopaedic surgery can undergo such surgery with a high expectation of success [11]. Thorough analysis of each case as part of a multidisciplinary team will allow us to perform elective orthopaedic procedures in patients with inhibitors. In Madrid, a total hip arthroplasty (THR) was performed in a 50-year-old patient after a displaced fracture.

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**Fig. 20.1** A 32-year-old haemophilic patient with severe haemophilic arthropathy of the left hip: (a) radiograph during childhood; (b) radiograph before the implantation of a cemented Charnley total hip arthroplasty; (c) position of the patient on the operating table; (d) intra-operative view of the renaming of the acetabulum.
of the femoral neck. As the fracture was diagnosed 6 days after the patient's fall, it was decided to carry out a THR instead of a hemiarthroplasty or an open reduction and internal fixation (ORIF) of the fracture. The high risk of avascular necrosis of the femoral head after ORIF and the high risk of prosthetic loosening of a hemiarthroplasty made us decide on THR as
the best solution. In the short term (2 years) the result has been excellent.

Authors’ experience

During 1976–2001, 23 total hip arthroplasties were performed in 22 haemophilic patients (Figs 20.1 and 20.2). The indication for THR in people with haemophilia was severe disabling pain, both during activity and at rest, that was unresponsive to non-operative treatment. The mean age of the patients was 32 years (range 21–49 years). At the time of the index hip arthroplasty, two patients were seropositive for HIV. The mean duration of follow-up for all the patients was 10.5 years (range 1–24 years).

Three patients died before the time of this review, and 19 were alive. Twenty patients had factor VIII deficiency, and two patients had factor IX deficiency. One patient had inhibitors. Two patients have undergone revisions for aseptic loosening. One patient has had three revision procedures: two for acetabular loosenings, one for a femoral component loosening. The other patient had revision for an acetabular loosening problem. Eleven hips had cementless fixations and 12 had cemented fixations. There were no infections in this group.

Conclusions

The authors’ experience (23 hips) and the review of the literature (140 hips) have shown the benefits of THR in haemophilic patients (Table 20.1), although the rate of complications is higher than in osteoarthritis. Careful counselling and education of both patients and health-care workers before operation are therefore essential. The results are inferior to those obtained in osteoarthritis, and the incidence of complications is higher for those who are seropositive for HIV. Despite the complications, this operation has a continuing role in the treatment of haemophilic arthropathy in patients who have severe pain and disability.

Total hip arthroplasty in people with haemophilia should only be performed in major centres with experience in managing these patients [12]. In addition to thorough preoperative medical preparation of the patient, considerable surgical preparation is also required. Depending on the age at which significant bleeding began, the proximal anatomy of the femur can be distorted and, in the most severe cases, there can be an extremely small femoral medullary canal, valgus and excessive anteverision of the head and neck, and protrusio acetabuli.

Table 20.1 Main series of total hip replacements (THRs) in haemophilia published in the literature.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of THRs</th>
<th>Year of publication</th>
<th>Reference</th>
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<td>Luck &amp; Kasper</td>
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<td>1995</td>
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<td>Löfqvist et al.</td>
<td>13</td>
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<td>Heeg et al.</td>
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<td>1998</td>
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<td>Takedani et al.</td>
<td>9</td>
<td>2000</td>
<td>[6]</td>
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<td>Hicks et al.</td>
<td>27</td>
<td>2001</td>
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<td>Rodriguez-Merchan et al.</td>
<td>23</td>
<td>2003</td>
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References

Total knee replacement in the haemophilic patient


Introduction

As a result of repeated articular bleeding episodes from early childhood, haemophilia patients commonly have an advanced degree of knee joint damage by the time they reach adulthood. Initial stages of the haemophilic arthropathy of the knee can be successfully managed with a combination of medical treatment and physical therapy. However, the patient will often present to the orthopaedic surgeon with advanced stages of arthropathy characterized by pain, restricted range of motion, a certain degree of deformity and severe functional disability. The transfer of increased stresses from the affected knee to other involved joints, such as the contralateral knee and the ipsilateral ankle, is likely to increase functional disability [1]. Incapacitating knee pain, not responding to medical treatment, associated with an impaired function is clearly an indication for total knee replacement (TKR) in a haemophiliac patient. There are many reports of successful orthopaedic surgery, including total knee arthroplasty (TKA), in haemophilia patients. Compared to the general population, TKRs in haemophiliacs are technically more challenging, as a result of extensive arthrofibrosis and bone deformities, and appear to have an increased rate of late infection. Some authors relate this phenomenon to an immune suppression resulting from human immunodeficiency virus (HIV) infection. Considerable controversy exists over this issue and some authors question whether the benefits of TKR outweigh the reported higher risk of late infection in patients with symptomatic HIV infection and/or acquired immune deficiency syndrome (AIDS). However, excellent long-term results of TKRs in HIV-positive haemophiliacs have been reported and, given the severe impairment with advanced arthropathy, many haemophilia centres are performing TKA in both HIV-positive and -negative patients. This encouraging clinical experience is broadening the indications for knee replacement in this population.

Primary total knee replacement in the general population

Clinical results

There are several reports pertaining to the long-term survival of modern design cruciate-retaining and posterior stabilized total knee components in the general population. A pooled analysis of 1342 TKRs performed with cruciate-retaining components (Press-Fit Condylar (PFC), Anatomic Graduated Components (AGC), Miller-Galante), considering revision for any cause as the endpoint, shows a 10-year survival between 84.1 and 97.3% [2]. The 15-year survival free of revision of 4583 cases performed with the AGC TKR have been reported to be 98.7%. Reported 15-year survival for 168 Kinematic I condylar knees and 501 PFC knees was 85.1 and 95.5%, respectively. A 91% 20-year survival was reported with the Total Condylar prosthesis. Similar results have been indicated for posterior-stabilized TKRs. The 10-year survival, free of revision for any cause, of the Insall-Burstein II and the PFC TKRs have been described to be 92 and 95.5%, respectively. The role of the posterior cruciate ligament in knee replacement remains controversial. Kinematic studies of cruciate-retaining and cruciate-substituting designs have demonstrated that both designs have abnormal kinematics. These design variations are approximately equivalent in clinical results.

A survival rate of 78%, considering any revision as the endpoint, has been described in younger patients. These results are clearly inferior to those in more elderly patients. Thus, TKR should be used with caution in younger patients whose activities are not limited by polyarthropathy or other debilitations of chronic disease.

Prosthetic infection in total knee replacement

The rate of infection after a TKR among the general population, with the use of modern techniques of asepsis and antisepsis, have been reported to be between 1 and 2%. Diagnosis of infection
in a TKR is usually made by aspiration and culture but false-negative cultures are not uncommon. Mason et al. [3] found the synovial fluid leucocyte count and differential analysis to be a statistically relevant indicator of the presence of infection. A synovial aspirate with a white blood cell count of at least 25 000 cells/mm$^3$ and at least 60% polymorphonuclear cells is highly suggestive of infection (specificity 95; sensitivity 98%). Indium scan in the diagnosis of infection at the site of TKR has a sensitivity of 77%, a specificity of 86%, positive and negative predictive values of 54 and 95%, respectively, and an accuracy of 84% for the diagnosis of infection.

The treatment of infection after TKR is a controversial issue, especially in the immunosuppressed patient. Two-stage re-implantation with the use of a static antibiotic-impregnated cement spacer is the more accepted method of treatment. It has a 10% rate of re-infection and a 90% rate of good and excellent results following the second stage. Preoperative aspiration of the joint and culture of the specimen before second-stage re-implantation is useful for defining the risk of recurrent infection. Patients with positive cultures should be treated with repeat débridement and re-insertion of antibiotic cement spacer or knee fusion. The ability to return to normal activities is less in patients who have had revision for infection.

Stemmed components are an important consideration in revision knee arthroplasty. The rate of failure after revisions performed with primary knee components is 26%, as compared with only 3% after revisions with stemmed implants designed for revision arthroplasty. This suggests that primary non-stemmed implants should be used very cautiously in the revision setting.

**Total knee replacement in haemophilia**

**Conservative management and débridement**

Prior to considering TKR, the patient should embark on a diligent programme of restorative physical therapy focusing on range of motion and strengthening combined with non-steroidal anti-inflammatory drugs. Some patients will achieve

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Fig. 21.1 Total knee replacement in a 32-year-old HIV-positive haemophilic patient with severe and very painful haemophilic arthropathy: (a) Anteroposterior (AP) preoperative view; (b) lateral preoperative view.
significant improvement on this regimen. For those patients who continue to be symptomatic, the preoperative strengthening will greatly facilitate postoperative recovery and improve the end result. For some younger patients, joint débridement may be useful. Although débridement should not be looked upon as an alternative to TKR, it should be considered in the young haemophilic to avoid, or delay, TKR. The operation may give the patient years of life without pain. When débridement fails to relieve pain, replacement must be considered.

In 1994, Rodriguez-Merchan et al. [4] described 11 open knee débridements in 11 patients suffering from advanced haemophilic arthropathy of the knee. Follow-up was for an average of 5.4 years (range 2-11 years) and the mean age of patients was 28.7 years (range 25-42 years). The clinical results were excellent in four, good in five and fair in two.

**Surgical technique**

The presence of arthrofibrosis and reduced bone stock requires a thorough assessment before undergoing TKR in a haemophilic patient (Fig. 21.1). Severe arthrofibrosis makes the surgical exposure more challenging and time-consuming. If this is the case, extensive releases as well as débridement are usually required in order to evert the patella and obtain adequate flexion to prepare the distal femur. Making the tibial cut first usually improves the exposure; however, care must be exercised to avoid injury to popliteal neurovascular structures. Usually, adequate débridement allows the femoral cut to be made first. This will allow retractors to be placed behind the tibia before making that cut which improves exposure and protects the popliteal structures.

Special attention should be given to patients with advanced arthropathy, in whom extensive joint surface erosion and periarticular synovial cysts are present. Large synovial cysts and other forms of bone stock deficiency increase the risk of intra-operative fracture. Structural defects in the distal femur or proximal tibia are bone grafted using local bone removed in TKR preparation. Large grafted defects are bypassed with a stemmed component to reduce the risk of pathological fracture. If the patient has a severe flexion contracture of the knee, additional bone should be removed from the distal femur. However, the patellar tracking should be carefully assessed in order to avoid 'patella baja'. Posterior capsule releases are often sufficient to correct small flexion contractures. The capsule is released from the distal femur under direct vision.

In patients with very limited preoperative range of motion, quadricepsplasty should be considered. The resultant length of the extensor mechanism is a critical factor in the rehabilitation; overlengthening the extensor mechanism should be avoided in order to prevent a permanent extensor lag.

Substantially decreasing the risk of postoperative haemarthrosis following TKR may reduce the risk of infection, patient morbidity, the length of stay in the hospital and costs. This may be especially helpful in haemophilia. Since 1972, fibrin sealants have been increasingly used as haemostatic and sealing agents in a variety of surgical procedures [5-7] including, recently, TKR [8,9].

A randomized controlled trial by Wang et al. [10] has shown that the use of fibrin sealant in non-haemophilic patients undergoing TKR significantly reduces the amount of blood loss through the postoperative drains, when compared to the use...
of standard means of haemostasis. The postoperative haemoglobin levels are higher in patients treated with fibrin sealant, which translates into lower blood transfusion requirements. These results suggest that the use of a fibrin sealant is a safe and effective means to reduce blood loss and transfusion requirements following TKR, which could play a significant part in patients prone to excessive bleeding, such as haemophiliacs. According to Wang et al. [10], fibrin sealant may facilitate more aggressive anticoagulation to reduce the prevalence of postoperative deep-vein thrombosis, pulmonary embolus and death following TKR. Their study confirms the viral safety and low rate of complications associated with fibrin sealant.

Postoperative drains are routinely used. The role of continuous passive motion after TKR has been a matter of controversy, but in this population may be useful, especially prior to physical therapy. An aggressive programme of physical therapy should be started while the patient is in the hospital, and should be continued as an outpatient 5 days a week for the first 2–3 weeks, and 3 days a week thereafter for 6–9 weeks. If necessary, knee manipulation should be performed between postoperative day 7 and 10, after the wound has begun to consolidate and before significant adhesions have formed.

Clinical results

In 1985 Lachiewicz et al. [11] published the results of 24 TKRs in 14 patients, reporting five complications: two late infections, one subcutaneous haematoma, one case of haemolytic anaemia and one patient who developed an inhibitor. The average age was 35 years and the follow-up was 2–9 years. Results were excellent in 15 knees, good in six, fair in one and poor in two. In 1988, Karthaus and Novakova [12] reported 11 TKRs in eight patients with a follow-up of 2–8 years. Ten patients suffered postoperative complications: epistaxis, haemarthroses, ana-phylactic reaction, urinary tract infection with haematuria, recurrent phlebitis at the site of venipuncture, and fever of a few days’ duration. Results were excellent or good in nine knees, fair in one and poor in one.

Wiedel et al. [13] published a report of 97 TKRs in 76 patients, showing a progressive increase in acute infections. The authors also noted a higher risk of infection in HIV-positive
patients. This latter finding was supported by the findings of a 1993 study by Gregg-Smith et al. [14]. A high risk of secondary infection in HIV-positive patients led the authors to recommend that TKR be carried out only in a select group of patients. However, Birch et al. [15] reported only one infection after 15 TKRs performed in haemophiliacs (eight of whom were HIV-positive). The infection developed 5 years after the surgical procedure, after the patient suffered a haemorrhage that occurred at the same time as a dental infection. Thus, in contrast to the findings of the previous study, the authors encouraged the use of TKR, emphasizing that the procedure did not carry an increased risk of postoperative infection. However, they added that in patients with a low CD4 count, the HIV infection was likely to progress.

In a multicentre survey by Ragni et al. [16], carried out in 115 centres from 37 states across the USA, the rate of postoperative infection in HIV-positive haemophilia patients with CD4 counts of < 200/mm$^3$ was higher than in the non-haemophilia population. Of a series of 27 TKRs, eight (30%) became infected. Such figures are considerably higher than the rate of infection in the non-haemophilia population. The authors concluded that the decision to carry out total joint arthroplasty in haemophiliacs with CD4 counts < 200/mm$^3$ should be made only after a thorough analysis of the risk:benefit ratio.

Unger et al. [17] performed 26 knee arthroplasties in 15 patients with haemophilia A and HIV infection from 1984 to 1991. Patient age range was 27–48 years. After an average follow-up period of 6.4 years (range 1–9 years), all patients were alive and none of the implants had become infected. CD4 lymphocyte counts showed some deterioration, which was not clinically significant. All of the patients were improved following surgery. Nineteen implants were rated excellent, four good and three fair. Infection with HIV did not adversely affect the clinical outcome of knee arthroplasty at follow-up periods up to 9 years.

Löfqvist et al. [18] published six cases of TKR with only one infection (an HIV-positive patient) who eventually required a knee arthrodesis. In 1997, Phillips et al. [19] performed a study aimed at determining whether major orthopaedic surgical procedures accelerate the fall of CD4 lymphocyte counts of patients with haemophilia who were infected with HIV, and whether patients who underwent surgery had different rates of progression to AIDS or death compared with patients who did not have surgery. A total of 61 surgical procedures were performed, including 14 TKRs. The results of the 14 TKRs were satisfactory. There seemed to be no evidence to suggest an acceleration in the rate of CD4 lymphocyte decline in HIV-positive patients with haemophilia as a result of elective joint surgery. Furthermore, elective joint surgery on HIV-positive patients with haemophilia did not affect the rate of AIDS development or influence mortality. However, despite this favourable conclusion, the authors expressed concern that the general prognosis of a patient’s HIV-related illness may be adversely affected by the physiological demands of major surgery or any subsequent sepsis on an already severely depleted immune system.

Heeg et al. [20] evaluated the long-term results of three total hip and nine total knee arthroplasties in nine haemophilic patients with disabling pain and end-stage arthropathy. These patients were followed over a period of 2–12 years (mean 6.9 years). One patient had a postoperative haematoma, which was evacuated, and two patients required manipulation of the knee because of limited range of motion. There were no infections. At follow-up, all patients were completely free of pain except two who had occasional pain. The functional improvement was impressive with an average increase in the knee score from 37 to 80 points postoperatively. The hip score increased from 36 to 85 points. The range of motion was increased in seven joints, unchanged in two joints and decreased in three. One total knee demonstrated non-progressive radiolucency. Median consumption of coagulation factor concentrate in severe haemophiliacs decreased from 47 000 IU/year (range 16 000–144 000 IU/year) before surgery, to 25 000 IU/year (range 18 000–132 000 IU/year) at 2 years after surgery. The authors concluded that knee arthroplasty is a valuable option in symptomatic haemophilic patients with disabling arthropathy, in order to obtain pain relief and functional improvement. It is associated with a low rate of complications and may reduce the need for substitution of factor VIII and factor IX.

Recently, Thomason et al. [21] published a report on 23 TKRs in 15 patients with a mean follow-up period of 7.5 years and a minimum of 4 years for patients who were alive ($n = 8$) at the time of their review. All seven patients who died before review were HIV-positive. Using the Hospital for Special Surgery (HSS) knee scoring system, the result was excellent in one knee, good in three, fair in two and poor in 17. There were two early and two late deep infections, all in patients who were HIV-positive. One knee had to be revised for aseptic loosening.

Schick et al. [22] studied how the known clinical effects of TKR in haemophiliacs translate into improved quality of life, as measured with validated condition-specific and generic questionnaires (Knee Society Score, WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index, developed by the University of Western Ontario, London, Canada), SF-12, transition questions), addressing physical, mental and social health. Eleven patients (13 knees) undergoing TKR from 1986 to 1994, with the diagnosis of severe haemophilic arthropathy of the knee, were followed-up over a 4-year period on average. TKR was found to reduce the burden of disease to levels similar to patients with osteoarthritis undergoing hip arthroplasty. Clinical and functional improvement after TKR translated into a substantial and significant increase in quality of life and patient satisfaction, found in objective as well as in patient-perceived measures. However, the physical functional ability did not reach the same level as in the corresponding population not affected by haemophilia, because of residual symptoms and impairment of other joints.

Vastel et al. [23] tried to determine the effect of factor replacement rate and HIV disease on results and complications in TKR in haemophilia. Twenty-nine total knee arthroplasties were performed in 21 disabled patients with severe haemo-
Three different types of prostheses were used. A follow-up with classical haemophilia who underwent 21 TKRs. The evaluation was undertaken between 2 and 10 years after the operation (mean 5.6 years) and two patients with infection were excluded. Knee scores averaged 77.5 (preoperative 24.1) and functional scores averaged 84.4 (preoperative 23.2). There were no cases of aseptic loosening of the prosthesis. Complications included one early deep infection treated by conversion of the TKR to an arthrodesis; one case of late septic loosening that had to be re-operated upon; one case of patellar dislocation; two cases of stiff knee (fibroarthrosis) that required manipulation under anaesthesia; one postoperative hepatitis; one superficial infection treated by incision and drainage; and four febrile patients with no clear source of infection who responded to antibiotics alone. The authors concluded that, despite a higher incidence of complications than other arthropathies, TKR offers haemophilic patients reliable relief of pain, reduction in joint bleeding and a long-lasting improvement of their quality of life, and therefore advocate its use with the appropriate indications.

Solimeno et al. [25] reported on 61 knee replacements on 51 patients performed between 1993 and 2001. Fourteen of the patients were HIV-positive with CD4 counts > 200/mm³. Five of the patients had high responding inhibitors. Using the HSS rating system, results were 21 excellent, 20 good, five fair and five poor. There were three deep infections, two of which were in HIV-positive patients. The inhibitor group had one deep infection and one aseptic loosening.

Recently, Hicks et al. [26] published a report on 102 replacement arthroplasties in 73 HIV-positive patients from eight specialist haemophilia centres. Of these, 91 were primary procedures. The overall rate of deep sepsis was 18.7% for primary procedures and 36.3% for revisions. There were 74 replacements of the knee.

Norian et al. [27] reported a retrospective review of the results of 53 TKRs performed in 38 haemophilic patients, 29 of whom were seropositive for HIV. The 5-year survival of the prostheses was 90%. The most common cause of failure was infection (seven knees), which developed at an average of 60 months (range 3–138 months) after the arthroplasty. The CD4 lymphocyte counts of patients in whom infection developed was not significantly different than that of patients in whom it did not. The HIV status also did not appear to be related to the development of infection. Authors concluded that TKR in haemophiliacs has a high risk of failure as a result of infection, although the infection is likely to be late and related to haematogenous spread during administration of coagulation factor.

Rodriguez-Merchan and Wiedel [28] reported a retrospective review of 37 TKRs, performed on 26 men from March 1975 to November 1995. The HSS knee rating scale was used as follows: 85–100 excellent, 70–84 good, 60–69 fair and < 60 poor. HIV-positive patients were evaluated to assure a stable medical status. A CD4 count of ≥ 200/mm³ was considered appropriate for surgical treatment. Sixteen of 26 patients had a prior surgical history of arthroscopic or open synovectomy. Overall, 22/26 (84%) of the results were good to excellent, 2/26 (8%) were fair and 8% (2/26) were poor. The mean pain score improved from 11 preoperatively to 28 postoperatively, where a score of 30 meant no pain. The improvement in pain levels showed the
most dramatic improvement of all categories. Knee function was graded on a scale with a 22-point maximum; patients improved from a mean of 12 preoperatively to 17 postoperatively. The majority of these patients were HIV-positive (n = 17) and, of these, nine died from complications of AIDS. Mean survival time for HIV-positive patients was 113.8 months (9.6 years) after surgery, with a range of 3–16 years. HIV-positive patients tolerated surgery well and there was no significant decline in the HIV wellness scale temporarily related to the surgery. Although the frequency of recurrent haemarthroses is usually much less in adults with advanced destructive arthropathy, nearly 70% of patients (16/26) in this study reported a preoperative history of recurrent haemarthrosis ranging from one or two episodes per year to two or three per month. During hospital admission, the total factor given ranged from 23 500 to 111 292 units per patient. After discharge from the hospital, 21 patients reported complete cessation of haemarthrosis in the replaced joint, three patients indicated that they experienced infrequent haemarthroses (one to two per year) and these responded well to factor administration. However, two patients required a partial synovectomy to control frequent recurrent bleeding episodes which persisted following total knee arthroplasty. Overall, there were 28 complications in 35 joint replacements. Complications included haemarthrosis, arthrofibrosis, superficial wound infection, joint sepsis, wound dehiscence, peroneal nerve palsy and prostatic loosening.

Complications were subdivided into early or late postoperative complications. Early complications included severe haemarthrosis in five patients (2/17 prior to 1986 and 3/18 after 1986); four were treated uneventfully with arthroscopic washout and one with open lavage. Two partial peroneal nerve palsy, recognized in the immediate postoperative period, resolved. Failure to regain motion, which required manipulation under anaesthesia, occurred in 12 patients (13/17 knees) prior to 1986, and in four patients (4/18 knees) after 1986. This may reflect the change to more aggressive factor replacement. If manipulation under anaesthesia was performed, it was generally done within 1–2 weeks of the TKR. The decision to manipulate was based on failure to gain 60–70° of flexion during the 2-week postoperative period. One wound dehiscence occurred during manipulation under anaesthesia.

Infection is the late complication of most concern. A superficial wound infection occurred in one patient and resolved with irrigation, débridement and antibiotics. Of more concern were bilateral deep articular infections, which developed in two HIV-positive patients who had CD4 counts of < 200/mm³ at the time of occurrence. The onset of infection was delayed and occurred 2 years after each respective total knee arthroplasty. In each case of infection, there was a documented distant source of infection (dental abscess, sinusitis or contaminated needle use). The first patient, who received a right cemented component in 1983 and a left uncemented component in 1986, developed a documented Staphylococcus aureus infection in both knees in 1988. Initially, the bilateral knee infection responded to arthroscopic irrigation and parenteral antibiotics. However, in 1990, the patient had a Staphylococcus aureus infection of the right knee, and a two-stage salvage procedure was performed with a good result. Bilateral TKR was performed in the second patient in 1982, with the right side uncemented and the left side cemented. In 1984 and 1988, a Staphylococcus aureus infection arose in both knees. Eventually, this patient went on to attempted knee fusion ending in non-unions, but functional resection arthroplasties. Two knees were re-operated for loosening, one with progressive bone–implant interface radiolucency and the other with varus subsidence of the tibial component to approximately 20°. The index arthroplasties in these cases lasted for 11 and 12 years. Both were uncemented implants.

Silva and Luck [29] reported the results of 90 primary TKRs, performed between 1975 and 2001, which were followed for a minimum of 1 year (mean 7.5 years; range 1–25 years). The clinical data was reviewed retrospectively. Knee Society (KS) clinical and functional scores were obtained at follow-up. Mean age at arthroplasty was 40 years (range 18–70 years). Sixty-three cases (70%) were HIV-positive and 27 (30%) were HIV-negative. CD4 count was obtained in 44 of the 63 HIV-positive patients, averaging 426/mm³ (range 33–1260/mm³). Postoperative complications were observed in 13 cases: eight postoperative haemarthroses, three Coombs-positive haemolysis, one non-fatal pulmonary embolism, and heterotopic ossification that occurred bilaterally in one patient.

An average preoperative flexion contracture of 19° improved to 9° postoperatively (P < 0.0001). The range of motion measured at the latest follow-up was, on average, 13% higher than the one recorded preoperatively (P = 0.0002). Seven cases required removal of the components: four cases for late infection (average 53.1 months; range 11.9–111.3 months), two cases for aseptic loosening (one knee with loose first generation components, and one knee with femoral component loosening secondary to a supracondylar femoral fracture resulting from a fall) and one case for recurrent haemarthrosis caused by synovial impingement under a well-fixed patellar component. Of the infected cases, two underwent arthrodesis and two resection arthroplasty. Both cases of aseptic loosening were revised. In the case with recurrent haemarthrosis, the patellar component was removed. Besides the four infected cases that required removal of components, seven knees that became infected were treated with irrigation and débridement without removing the components. Infection was persistent in two of these cases. No early postoperative infections were observed. Staphylococcus aureus and epidermidis accounted for 73% of the infections. The incidence of infection in HIV-positive and HIV-negative patients was 14 and 11%, respectively, which was not statistically different (P = 0.8). No correlation was found between CD4 count at surgery and infection (P = 0.8). Considering component removal or radiographical loosening as endpoints, Kaplan–Mayer survival analysis indicated a 10-year survival rate of 92% (95% CI; range 85–89%). Considering component removal or persistent infection as endpoints, the 10-year survival is 87% (95% CI; range 75–95%). Excellent and good clinical scores were obtained in 76% of
Table 21.1 Review of the literature.

<table>
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<th>Authors</th>
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<td>[16]</td>
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<td>26</td>
<td>1995</td>
<td>[17]</td>
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<td>6</td>
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TKRs, total knee replacements.

the cases. Fair and poor clinical results were related to limitations in range of motion, especially in the case that developed heterotopic ossification postoperatively. However, this limitation in range of motion did not limit functionality, as shown by the functional scores which were excellent and good in 96% of the cases. Authors concluded that although the incidence of infection after a TKR is higher in haemophiliacs than in the general population, possibly related to frequent self-infusion of clotting factor, the benefits of this procedure are substantial and must be weighed against the risk.

Theoretically, the alternative to TKR is arthrodesis. Its main indications in haemophilia are unilateral haemophilic arthropathy in a young person without haemophilic arthropathy in another joint of the lower limbs, multiply operated knee, painful ankylosis and failed TKR. Currently, the most frequent indication for knee fusion is the failed TKA, especially with persisting infection [30]. Fusion should be considered an irreversible procedure and should be performed selectively, especially in the light of modern arthroplasty. Compression arthrodesis and intramedullary rod fixation can be used, each of which has a role in these difficult cases. In patients with longstanding fibrous ankylosis, arthrodesis is likely to produce a predictable good result whereas TKR may result in poor range of motion with no advantage over arthrodesis and with the risk of late infection.

In joint replacement terms, the follow-up of most published series is generally short. Ten years’ follow-up is needed to confirm the reported results. The rate of loosening and infection will probably increase over time.

Conclusions

Total knee replacement for advanced haemophilic arthropathy has good and excellent results in about 85% of cases (Table 21.1). The principal risk is late infection, which can occur regardless of HIV status. However, this risk appears increased in the patient with a CD4 count < 200/mm³. Although the message of this Chapter may seem conservative, it should not be inferred that a TKR should be avoided in an HIV-positive haemophilia patient today, but that the orthopaedic surgeon, treatment team and the patient should weigh the risks and benefits carefully [31–33]. These authors’ experience (about 250 knees) and the review of the literature (about 350 knees) have shown the benefits of TKR in haemophilic patients (Table 21.1).

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THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES


Elbow arthropathy in patients with severe haemophilia

N.J. Goddard

Introduction

There is a relative paucity of literature concerning haemophilic elbow arthropathy, with much information being confined to single case reports or small studies. The elbow is the second most common site for arthropathy in the haemophilic patient. Destructive changes occur insidiously but, because it is not a weight-bearing joint and function is not dependent on the extremes of movement, such limitations of flexion and extension seldom significantly impair overall function [1].

Attempts have been made to identify those patients at the highest risk following elbow bleeds. Aronstam et al. [2], in a study of adolescents with haemophilia A, concluded that elbow haemarthroses presenting with pain and tenderness with a loss of > 50% range of motion are likely to have a poor long-term prognosis. A delay of more than 3 h from onset of symptoms is associated with a poor response to factor VIII therapy.

The course of haemophilic arthropathy is well described with repeated bleeds leading to chronic synovitis with extensive joint surface erosion and ultimately to end-stage joint destruction. Arthrofibrosis and loss of motion further complicate end-stage arthropathy as the hypertrophic synovium is replaced by dense fibrous scar tissue [3]. Severe contractures, deformities and architectural distortions are commonplace.

At the elbow there is an increasing restriction of movement, especially prono-supination, and a slow increase in the degree of pain. The progressive joint destruction often results in marked elbow instability and occasionally a tardy ulnar palsy. The early radiological changes include loss of joint space and subchondral irregularity. Radial head enlargement is seen relatively early, contributing to limitation in forearm rotation (Fig. 22.1).

In advanced elbow arthropathy, the olecranon notch may become enlarged as the humerus appears to erode through the ulna (Fig. 22.2), and there may be associated widening of the radial notch of the ulna [1,4]. There have been no comprehensive correlative studies between radiological and clinical findings in severe haemophilic elbow arthropathy.
Clinical assessment

We have recently carried out a clinical and radiological assessment of a group of 26 patients attending the Haemophilia Unit at the Royal Free Hospital, London, with severe haemophilic arthropathy of the elbow. The majority had a functional range of motion which permitted them to manage standard activities of daily living including carrying moderate weights and managing personal hygiene.

All patients underwent subjective and formal objective assessment. There is no specific scoring system applicable to haemophilic joints, but the Hospital for Special Surgery (HSS) rating as described by Inglis and Pellicci [5] is perhaps the most appropriate, despite its limitations as highlighted by Pynsent et al. [6]. Four patients were classified as having severe impairment of movement or no movement in their elbows. Two patients had fairly advanced arthropathy with severe restriction of flexion and extension but had so far declined surgery. One patient had bilateral elbow involvement.

It is important not to regard the elbow in isolation. We took care to assess the presence of other joint involvement in the upper limb which may have affected the global clinical and functional assessment. Patients graded the shoulder, elbow and wrist joints on both sides from 1 to 6 (1 worst/6 best). In patients in whom the elbow joint was the worst affected, about 25% of these also had significant involvement of other joints. There was more of an overlap in patients who had moderate or slight affliction of the elbow. It was clear that involvement of the shoulder or wrist caused significant interference in the assessment by patient questionnaire of the elbow joint. In particular, this affected activities of daily living such as lifting a bag of shopping. At least two patients had more severe shoulder arthropathy, making the carrying of any weight difficult.

Radiological assessment

Several classifications for haemophilic arthropathy have been described based on both clinical and radiological findings [7]. Such classifications and those proposed by Wood et al. [8] in 1969 have not proved satisfactory for assessing effects of modern treatment nor, importantly, the prognosis.

Pettersson et al. [9], in 1980, proposed a radiological classification of changes in haemophilic arthropathy with a possible joint score between 0 and 13, with ankylosis alone scored as 13 points. This classification is now widely accepted by the World Federation of Haemophilia and is used by many researchers studying outcome measures in haemophilia. However, this scoring system has its limitations in patients with haemophilic arthropathy, largely because of the multijoint involvement and complicating factors.

Eighty per cent of radiographs displayed medial osteophytes or spurs (Fig. 22.3). Radial head enlargement and joint space narrowing was seen in 50% of cases. Deepening of the notch on the ulna at the superior radio-ulnar articulation was seen in 25%, which was commonly associated with restriction of pronation. Seldom did we see evidence of premature epiphyseal fusion, growth arrest lines, the presence of an isolated cyst or epiphyseal enlargement.

Findings

We attempted to find any reliable correlation between the clinical and radiological features in an attempt to further understand the natural history of the condition. There was no statistically significant association (95% confidence level) between the frequency of bleeds with radiological features such as subchondral damage, narrowing of joint space, erosions and deformity. However, pain had a better association with erosions and sclerosis and were significant at the 90% level but not at the 95% confidence level.

The range of joint movement appeared to have a strong relationship with severe joint narrowing, the presence of two or more cysts and subchondral damage. However, sclerosis had a low association with a loss of movement. There was a significant association between an enlarged radial head and a
deepening of the ulnar notch but, interestingly, this was not associated with a loss of prosupination.

In our study three main patterns of haemophilic arthropathy emerged upon analysis of serial elbow radiographs. The first pattern largely involved the humero-ulnar articulation as evidenced early on by a medial spur, a reduction in the humero-ulnar joint space, occasional subperiosteal new bone formation on medial aspect of the humerus and cysts again mainly on the medial side. Patients with these features appeared to have a higher incidence of ulnar nerve involvement: tingling in hands and weakness of intrinsic hand muscles for which ulnar nerve decompression was ultimately indicated. However, no statistical significance was found because of the small numbers in the cohort.

Secondly, patients with predominantly lateral joint involvement appeared to have symptoms and signs pertaining to the superior radio-ulnar joint: restriction of forearm rotation and posterolateral joint pain. Lateral joint changes on radiographs included enlarged radial head, reduced humero-ulnar joint space, formation of subchondral cysts and subperiosteal new bone formation on the lateral supracondylar humeral ridge. A proportion of these patients underwent synovectomy or radial head excision with satisfactory symptom relief.

A third distinct group of patients developed global osteoarthritic changes with generalized osteophytes, reduction in joint space and subchondral cysts. These patients exhibited diminution in all movements producing a very stiff joint. Some patients with this radiographical pattern have managed satisfactorily with a reduced arc of motion without requiring surgery. Disappointingly, but perhaps unsurprisingly, attempts at demonstrating probabilities of relationships between clinical features and specific radiological features showed no statistical significance.

**Medical management**

Nothing is better than prevention and ideally all patients should be treated with regular prophylactic factor replacement. However, we do not live in an ideal world and thus when faced with an acute elbow bleed the standard principles apply. Adequate factor replacement must be given, the joint is rested until the pain subsides whereupon physiotherapy and rehabilitation can begin. As a rule, the elbow is fairly quick to respond as it is a non-weight-bearing joint and, given prompt treatment, may be back to normal within a 24–48-h period.

There are mixed views concerning aspiration of an acute joint. Aspiration may be indicated if there is a tense haemarthrosis and also confers the additional advantage of removing blood and blood products from the joint as these may contribute to the development of arthropathy. Repeated bleeding episodes require a more aggressive approach. There have been encouraging results following synoviortheses, with the added benefit that patients did not require additional factor VIII replacement therapy during treatment [10].

Fixed contractures are difficult to manage and, unlike lower limb joints, the elbow does not respond well to physiotherapy or serial casting. However, Greene [11] reported that continuous passive motion was of some use in the rehabilitation of difficult paediatric knee and elbow arthropathy. A further safe alternative was proposed by Yates et al. [12] who demonstrated a decrease in flexion contracture of the elbow of almost one-third with the use of a Flowtron intermittent compression system. The authors did not administer prophylactic replacement during the study and hence recommend Flowtron in home treatment as a safe, inexpensive and effective treatment option for elbow contractures.

**Surgical treatment**

Surgical intervention should be considered with the onset of an established fixed flexion contracture with or without proliferative synovitis. In these cases surgical synovectomy combined with radial head excision and, possibly, anterior capsule release has been suggested [1,13]. The rationale for removing synovium from a haemophilic joint is similar to that in rheumatoid arthritis. Synovectomy removes a chronically oozing hypertrophied vascular bed and significant amounts of proteolytic enzymes such as cathepsin D. Synovectomy has been proposed as a means of controlling repeated haemorrhages rather than merely as a salvage procedure.

Gilbert and Glass [1] found that the effects of synovectomy were enhanced by excision of radial head at the same time, especially in patients with marked limitation in supination. Similar findings have been reported by Rodriguez-Merchan et al. [13] and ourselves (Fig. 22.4). The procedure is simple to perform, has few complications and generally results in a significant decrease in haemarthroses and pain with a significant increase in range of motion, especially prosupination, and thus ultimately function. Moreover, it resulted in a high degree of subjective patient satisfaction.

Kay et al. [14] reported results of synovectomy, without radial head excision, in patients with severe haemophilia and

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Fig. 22.4 Post synovectomy and excision of radial head.
concluded they had better outcomes in the 12 cases of elbow synovectomy than in patients who underwent knee synovectomy. Le Balc’h et al. [15] showed an improvement in flexion, extension and forearm rotation in their series of 23 elbow synovectomies in young haemophilic patients.

Isolated radial head excision has been shown to be an effective procedure in the treatment of haemophilic arthropathy of the elbow with or without synovectomy [1,16]. Luck [3] described the indications for radial head excision as being pain, chronic haemarthrosis unresponsive to non-operative management with disabling loss of rotation, mainly supination, and has claimed excellent pain relief and an improvement in supination of over 30°.

There are limited descriptions of total elbow arthroplasty in haemophilic arthropathy. Luck and Kasper [16] reported only two cases of elbow replacement in a total of 168 surgical procedures carried out for haemophilic arthropathy. We have performed this procedure on one occasion with an excellent outcome.

Nerve decompression procedures have also been described. Lancourt et al. [17] reported a series of 200 patients with haemophilia in which neuropathy was seen in only six. The most commonly affected nerve was the median nerve but in two patients the ulnar nerve was involved at the elbow, one as a result of a haemarthrosis of the elbow and the other because of a large medial synovial cyst. Lancourt et al. [17] postulated that intramuscular haemorrhage and subsequent oedema and fibrosis usually caused nerve involvement.

Conclusions

The HSS scoring system with regard to haemophilic elbows correlated reasonably with clinical findings but was not comprehensive, especially as a ‘spot’ score and cannot be regarded as a criterion for the requirement of surgery. This decision must be based upon clinical assessment and bleed frequency.

Certain radiographical features such as osteoporosis, deformity and incongruity, which are included in the Pettersson et al. criteria, were found to have a high index of inter-observer variability and therefore could not be relied upon. Radiographical features such as radial head enlargement, deepening of the radial notch, medial osteophytes, cysts and severe narrowing of the joint space correlated well with poorer elbow function. Radial head excision and synovectomy are procedures which confer patient satisfaction in terms of pain relief, reduction in bleed frequency and range of movement.

From this study it clearly emerged that surgery affected the natural history of the disease as seen in the correlation of HSS score with age in the dominant elbow after removal of operated cases. While this cannot be interpreted to suggest that early surgery should be undertaken in all cases in view of the small numbers in the study, it is an important finding. Le Balc’h et al. supported this view by demonstrating an improvement in the Pettersson et al. score in postsynovectomy patients and hence there has been a move away from more conservative approaches to the management of haemophilic arthropathy. A trend of earlier surgical intervention is reflected in Luck and Kasper’s work in the 1990s [16].

It was difficult to draw definite conclusions regarding the natural history of elbow arthropathy but clear patterns of radiological and clinical progression were observed. The medial joint involvement pattern was associated with loss of flexion and extension with preserved forearm rotation. The superior radioulnar and lateral joint involvement pattern was associated with lateral joint pain resulting in loss of rotation. Ultimately, these two patterns seem to progress into global osteoarthritis with associated stiffness and diminution of all elbow movements.

References

CHAPTER 23

Ankle arthrodesis in haemophilia

J. Galina and M.S. Gilbert

Introduction

Arthropathy at the ankle is a common cause of disability in the patient with haemophilia. According to Heijnen et al. [1] it is the second most commonly affected joint and, in our experience, it is the most commonly affected joint in patients under 20 years of age. Rodriguez-Merchan [2] has pointed out that the goal of treatment is restoration of function, allowing the patient to return to a normal lifestyle, as opposed to anatomical or radiographical correction. He groups treatments currently available into four broad categories: physiotherapy, orthosis, corrective devices and surgical interventions.

Radiological features

The radiographical changes at the ankle and hind foot have been well described by Pettersson and Gilbert [3] and Ribbons and Phillips [4]. The typical changes are seen at a young age and Ribbons and Phillips have pointed out that early episodic treatment has not abated the insidious deterioration. A common finding is narrowing of the lateral part of the distal tibial epiphysis. This has been shown to be true narrowing and not a result of the X-ray projection. Subchondral irregularity and cartilage space narrowing are frequently associated with significant anterior and posterior osteophyte formation. This is rather unusual in that osteophyte formation is not a prominent feature at the elbow and knee in patients with haemophilic arthropathy. Flattening of the dome of the talus is commonly seen. Total collapse of the body of the talus has been described [5]. MacNichol and Ludlam [6] have suggested that the changes in the talus are probably brought about by avascular necrosis and may arise secondary to impairment of the arterial supply as it enters the talar neck. Spontaneous ankylosis of the ankle joint has been reported by several authors [7–9]. Of clinical importance is the fact that subtalar arthritis is commonly seen with advanced arthropathy at the ankle, and this finding may influence the choice of surgical intervention.

Surgical intervention

It need not be emphasized that conservative treatment should be tried before surgical intervention is considered. This must include secondary prophylaxis, with judicious use of non-steroidal anti-inflammatory drugs, physical therapy, modification of footwear, and a custom-moulded ankle-foot orthosis to limit motion at the ankle and subtalar joints.

If conservative management fails, a variety of surgical procedures can be undertaken. These include Achilles tendon lengthening for equinus deformity of the ankle, arthroscopic ankle synovectomy and débridement is a viable alternative to open ankle synovectomy for controlling the frequency of bleeding and maintaining ankle function [10]. The patient with a large anterior tibial osteophyte with ankle pain aggravated by dorsiflexion may be treated by surgical excision of the osteophyte if the joint surfaces are reasonably congruent. This can be performed either open or arthroscopically. Because haemophilia is a progressive disease, the osteophyte may recur. Barring these alternatives, arthrodesis can eliminate pain, recurrent bleeding and correct deformity [11].

Luck and Kasper [10] report 18 cases of arthrodesis: 13 tibiotalar, four tibiotalar and subtalar, and one pantalar. Fixation techniques included internal fixation in 15 and Charnley external fixation in three. One tibiotalar fusion developed a painless non-union, and one subtalar fusion took over a year to consolidate. In cases of combined ankle and subtalar fusion, the tibia, talus and calcaneous were fixed with convergent cancellous screws.

The senior author of this chapter has participated in four ankle fusions and five triple arthrodeses. Three open ankle arthrodeses were performed with different techniques: Cross-Steinmann pin fixation, Charnley external fixation and convergent cancellous screw fixation. A fourth fusion was performed arthroscopically utilizing a burr to destroy the joint surface with percutaneous introduction of a cancellous screw through the fibula and another through the tibia. All ankle fusions were fixed in neutral position, and all were immobilized for 3 months or more in a short leg cast. The patients were instructed to remain non-weight-bearing for 6 weeks. At that time, the cast was changed and weight-bearing as tolerated started. The three
open procedures fused by 3 months. The arthroscopic procedure took 6 months to fuse. All triple arthrodeses were carried out to correct equinus and valgus deformity and all healed uneventfully.

Conclusion

It has been our experience, and that of most authors, that a fusion eliminates bleeding and results in a painless ankle joint. The main disadvantage is that the result may be temporary in that after several years the subtalar and mid foot joints may become symptomatic from overload in an effort to compensate for loss of ankle motion. This is more common in patients who have degenerative changes at these joints prior to ankle fusion and, for this reason, combined ankle and subtalar fusion has been suggested. Footwear with shock-absorbing materials in the sole and heel may delay this complication.

At the present time, arthrodesis remains the procedure of choice for patients with severe debilitating ankle arthropathy. There is scant literature on arthroplasty in the ankle in patients with haemophilia, and the potential benefits must be weighed against the possible sequelae of loosening infection and the need for consequent revision surgery.

References

Rehabilitation and physiotherapy
CHAPTER 24
Prevention and treatment of joint problems in children with haemophilia
L. Heijnen and P.J.M. Helders

Introduction

In childhood, the most frequent site of bleeding in haemophilia is the joint, followed by muscles and soft tissues.

Heijnen [1] describes the natural history and clinical course of severe haemophilia in relation to age. During the first year of life the child may develop haematoma after trauma, for instance on the forehead and the soft tissues of arms and legs, or after biting his tongue. When the child starts walking and falling, haemarthroses in ankles and knees occur. One hundred and sixty patients aged 4–26 years reported the following number of joint bleeds during a 1-year period: elbows 846; ankles 722; knees 648; shoulders 79; and hips 6. Hilgartner [2] describes range of motion deficits being apparent in the 1- to 5-year-old haemophilic child.

Rodriguez-Merchan [3] states that in small children the ankle is frequently the target joint. After the age of 5 years the knee joint has a more prominent role, and the non-dominant elbow joint becomes more problematic after the age of 5. He also mentions that in the course of haemarthrosis the abnormal synovium will act in a similar manner to that of an arteriovenous fistula, producing an excessive blood supply to the area of the epiphyseal plates. The excessive growth as a result leads to skeletal problems in young patients: leg length discrepancies, angular deviations and deformities of structures in the developing skeleton.

From the age of 10 to 17 years, there is a decline in knee and ankle haemarthroses whereas there is an increasing frequency of elbow bleeding [4]. Without replacement therapy, recurrent haemarthroses will lead to haemophilic arthropathy and an adolescent will have five damaged joints by the age of 20, while the degree of disability increases markedly with age up to 20 years [5]. However, in situations where primarily prophylactic treatment strategy is possible, patients only have a few joint bleeds per year (median 2.8), with low clinical scores (median 2.0) and low-grade arthropathy as measured by the Pettersson score (median 7 points).

The effects of long-term prophylactic treatment on bleeding frequency and prevention of haemophilic arthropathy have been extensively described in the literature [7–9]. However, 80% of the haemophilia population of the world does not have access to clotting factor replacement therapy. In this population, children with haemophilia will have recurrent haemarthroses leading to arthropathy and they are in need of treatment (such as physiotherapy and rehabilitation), as haemophilic arthropathy may limit daily childhood activities and social participation.

Review of the literature describing physiotherapy and rehabilitation

In the past, no clear distinction was made between rehabilitative measures for children and adults. However, most reports describe case histories and show pictures of children aged 10–20 years. Before factor replacement therapy was available, splints and casts of plaster of Paris were used to put the affected joint to rest, while Quengel and Wedge casts were used to correct flexion contractures [2,9,10]. For mild flexion deformities skin traction and balanced suspension were advised [10–12].

All these corrective measures were combined with quadriceps muscle drill and sometimes a lightweight night splint and a walking caliper or splint was used until knee extension was complete and the quadriceps muscle strength recovered. Acute haemarthroses with painful effusion were treated with rest and immobilization with a posterior plaster splint. After 24 h, static quadriceps exercises and active free flexion and extension were initiated, followed by partial weight-bearing and a night splint for 10 days [13,14]. All authors advise isometric quadriceps exercises followed after 12–24 h with isotonic and resistance exercises [13,15–18]. Boone [14] describes an anterior open thigh thermoplastic splint to support the leg during walking whenever the quadriceps is weakened. She also emphasizes the importance of patellar mobility, as do Benz and Krauss [19].

When mobilizing patients after an ankle haemarthrosis, Cole and Jones [13] describe a polypropylene ankle support that allows planar and dorsal flexion and Boone [14] describes a canvas anklet with medial and lateral metal straps. Driessen [10] protects the ankle with a C 1200 brace, which is a below-knee caliper with an ankle hinge, that attaches to the shoe. Different orthoses with hinges that may limit—e.g. hyperextension—are described [20].
Manual mobilization of the knee joint in cases of flexion contracture and posterior subluxation of the tibia is also described [19]. Benz and Krauss [19] also stress that special attention should be paid to exercises for the vastus medialis muscle with the knee in mid position. Weissman [21] uses hot-packs and the whirlpool to produce muscle relaxation to relieve pain. In case of chronic synovitis, intensive quadriceps drill has been instituted since the 1970s [22]. Martin-Villar et al. [23] describe an intensive programme with prophylactic replacement therapy three times a week and an exercise programme. They experience a 78% decrease in haemarthroses in 40 joints in 30 patients (11 patients under 10 years of ages, 18 between 10 and 20 years and one over 20 years.

Koch et al. [18] describe two case histories of children that compare aggressive strengthening techniques and restriction of physical activities with external support of the knee. It is the impression of the authors that strengthening rather than immobilization can bring about increased range of motion, increased strength and decreased bleeding frequency. Greene and Strickler [24] describe a modified isokinetic-strengthening programme for knee flexors and extensors, evaluated in 32 patients with severe haemophilia aged 5–51 years. The programme is effective in significantly strengthening the knee flexors and extensors. It does not increase the number of haemarthroses and can be done at home without special equipment. The greater increases in extensor and flexor strength among adolescents and adults are associated with less severe arthropathy, 1-cm increase in thigh girth and a greater number of days on which the exercises are done.

Desmarres and Laurian [25] describe functional problems in observed gait and movement of children with haemophilia, independent of muscular and articular deficit and discomfort. Pelletier et al. [26] describe a single-case experimental study with a 12-year-old subject with severe factor VIII deficiency and chronic knee arthrosis. The isometric exercise programme safely increases right hamstring and quadriceps femoris muscle group strength 40–70% without adversely affecting knee range of motion and without causing bleeding or discomfort. They conclude that the use isometric exercise programmes during rehabilitation and maintenance is a promising treatment component for the total care of the individual with haemophilia.

Pietri et al. [27] test the hypothesis that recurrent haemarthroses have an adverse effect on neuromuscular function. In 10 patients with haemophilia A and history of unilateral haemarthrosis of the knee, the uninvolved side was used as a control (age 14.1 ± 5.4 years). Neuromuscular function is evaluated on a Cybex 340 isokinetic dynamometer. The data show that these boys have neuromuscular dysfunction in the affected extremity preceding the appearance of radiological signs of joint pathology. The authors suggest that strength training should be started early in the rehabilitation of persons with haemophilia.

In recent literature, Buzzard [28] mentions several physical therapeutic modalities that are available and may help to prevent and treat the sequelae of recurrent haemarthroses. The use of active muscle strengthening exercises, hydrotherapy, physiotherapy techniques (including pulsed short-wave diathermy and ultrasound), ice and splints are extremely important, especially in developing countries where blood products are scarce. She also states that special attention should be paid to the training of proprioception as this has an important role in the control, timing and organization of co-ordinated bodily actions [29]. Buzzard also states that it is essential that people with haemophilia be taught the importance of physical fitness at an early age as a means of preventing articular contractures. As exercises can become tedious, especially for children, it is important to try and make physical activity more attractive by incorporating exercises into games.

Today, orthoses to correct knee contractures are still used in developing countries where replacement therapy is not sufficiently available. Kale et al. [30] describe the use of the dual-force system combined with active exercises in 10 patients aged 10–18 years. The mean duration of deformity is 10 months, mean range of movement at affected knee joints increased from 50° to 110° following 6 weeks of application of the dual-force system. It is of note that hardly any of the above mentioned reports are based on well-designed randomized controlled trials.

**Prophylactic exercises and sports**

Hirsch et al. [31] advise a home exercise programme for all persons with haemophilia and muscular skeletal residual impairment. Ideally, the person with haemophilia should be involved in a daily exercise programme, beginning in childhood [17]. At that time the advice does not seem as superfluous, because Koch et al. [32] find that 11 boys with haemophilia aged 8.3–15.5 years demonstrate poor exercise performance. Fricke [33] also advises lifelong daily exercises because strong muscles stabilize the joint and prevent haemarthroses. Baron [17] describes a specific exercise programme for teenagers and adults. Green and Strickler [24] describe a modified isokinetic strengthening programme for the knee extensors and flexors, which can be done at home without special equipment.

Hilgartner [2], Boone [14] and Weissman [21] mention the importance of participating in sports, with the exception of body contact sports, such as football and boxing. Capitano et al. [34] and Federici et al. [35] advocate skiing. Buzzard [29] states that very few limitations need placing on haemophilia patients choosing a sport. Karate, boxing and rugby are contraindicated because of the risk of head injury but most other sports, including football, skiing and cross-country running, are to be encouraged. Prophylactic therapy may be indicated for some patients. It is very important that each patient learns to recognize his own limitations and sometimes be advised to change sports because of evidence of an association between a particular activity and bleeding.

Heijnen et al. [36] studied physical activities and the participation in sports of boys and adults with haemophilia by means
of a self-administered questionnaire. All boys (41) under the age of 12 years participate in physical activity at school. Of 42 boys in the 12–17-year age group, only two of 28 boys with severe haemophilia and one of nine boys with mild haemophilia do not participate. In the younger age group there is no difference in frequency of attendance of physical education at school between boys with haemophilia and their classmates and there are only few differences in the activities they performed. Sports participation in the under-12 age group was 68% in cases of severe haemophilia and 100% for boys with moderate to mild haemophilia. In the 12–17-year age group the percentages are 77, 20 and 78%, respectively. Thirty-five boys under 16 years mention participation in the following sports: swimming 21, tennis 8, skating 8, table tennis 3, badminton 2, cycling 2, gymnastics 2, judo 2, soccer 2, street soccer 2 and other sports 7.

The changing panorama of paediatric rehabilitation

The focus of paediatric rehabilitation is increasingly changing. The emphasis on outcome measurement is the driving force, as outcome tells us ‘what’, while service provision determines ‘how’ it is provided. In addition, changing opinions on childhood development contribute to a different form of health-care intervention for children. In general, one could say that development is currently being viewed as the simultaneous combination of ‘to be’ and ‘to become’, meaning that it has to meet current needs (specificity) and future needs (plasticity). Such a view turns every paediatric rehabilitation process into a very dynamic one, with consequences for those involved.

For a long time the medical diagnosis was the leading element in paediatric rehabilitation. It became clear, especially during the last decades, that not the medical diagnosis but the functional consequences of a given disease or disorder were the key elements that needed to be treated. This triggered a whole cascade of developments, ranging from the development of a uniform language to describe those functional consequences (ICIDH (International Classification of Impairments, Disabilities and Handicaps) 1 and 2), to instruments measuring functional status in children and Quality of Childhood Life. From that, we learned that manifestations of disability in the first two decades of life differ from those in the adult years. Of great importance is the fact that variations in function and structure may be evidenced not only by deviations but also by delays in growth and development [37]. We are also beginning to understand the dynamic and reciprocal nature of person–environment interaction and its impact on childhood development.

All this has an impact on the way health care is structured and provided for children with disabilities. It is no longer ‘just a medical problem’, but a functional–developmental problem, which is significantly different in childhood. Functionally based treatment, focused on daily childhood living skills is necessary for age-appropriate programme planning, evaluation and documentation in both the clinical and educational environment.

Functional diagnosis in paediatric rehabilitation

The need for an accurate medical diagnosis is beyond any doubt; prognosis and, if necessary, counselling of the parents is highly dependent on that. However, parents should know ‘what comes after being diagnosed’. In paediatric rehabilitation, we are interested in the functional consequences of a given disease and/or disorder, and want to be supportive in solving problems that are functional and important to the child and family. Therefore, a functionally based age-appropriate developmental diagnosis is needed and should be thoroughly discussed with the parents. It is an important part of the total evaluation because it identifies what the child can accomplish in a given environment with or without assistive devices. Developmental problems are of a very dynamic nature, as every age has its own specific set of abilities and limitations. Functional diagnosis is therefore a cyclical event that needs to be documented carefully. It not only tells us the specific needs of the child at this moment and time, but also shows us the age-appropriate improvements of the child, provided the proper instruments are used. The perspectives of the parents are equally important. It is this combined perspective of the professional, the parent and the child that will give all the diagnostic information needed to start or adjust rehabilitation [38].

In our children’s hospital, we changed the traditional ‘gym’ into developmental movement scenery where the child is attracted to different kinds of movements appropriate for his age. It is a specially designed hall, equipped as a special playground, where all age-matched movement skills can be assessed with the help of valid instruments, e.g. the Movement ABC. Current literature increasingly suggests that not only the impairments, but also the functional capability should be the focus of rehabilitation efforts. Our treatment programme therefore not only corrects the range of motion or increases muscle strength, but also creates the opportunity for the child to participate in several movement activities where those functions have a key role. By participation in those activities, range of motion and muscle strength are ‘automatically’ addressed while cooperation of the child is guaranteed.

Family-centred care

One of the most important changes in the management of children with disabilities is the different orientation of the treatment strategies used: from impairment-driven and child-centred to functionally based and family orientated. This not only means an adjustment of the existing (outcome) measurement instruments (from an impairment domain to multidimensional domain), but also means the broadening of the total scope of
our invention. In recent publications it was found that family environment predicted outcome, after controlling for injury severity, and moderated the effects of traumatic brain injury in children [39]. In another study, researchers found greater developmental loss among children of parents with minimal amounts of social support [40]. This underlines the need for further investigation on whether improved family functioning leads to important clinical benefits for both children and families. Schoenmakers et al. [41] described 39 children with haemophilia who were found comparable with their healthy peers with regard to motor performance and activities of daily living (ADL). However, the majority (31/39) perceived an impact of their disease on their lives associated with pain (22/39) and restrictions in sports. This emphasizes that families with children with haemophilia need extensive counselling in what that medical diagnosis means for the functional status of their child. Restrictions in daily childhood activities are only then indicated when there is evidence that the child will benefit.

**Outcome-orientated care**

Outcome assessment can be defined as the systematic evaluation of the merits of health care in order to help patients, providers and payers to make rational choices, based on a better insight into the effect of health care on patients’ lives. It does not primarily focus on individual patients, but on patient populations. Standards of health care and outcome measurement are part of the quality of care cycle. Legitimacy and equity are equal parts of that same quality cycle. Established standards of care and/or quality standards can help to assess similar health-care programmes in different institutions for inter-institutional comparison of performance, not for the identification of ‘bad apples’ but in order to strive for continuous improvement of care. As has been established in paediatric rheumatology, we also have to build a core set of variables to determine whether individual patients have demonstrated clinically important changes over time in relevant domains of childhood functioning. The members of the paediatric rehabilitation team have to demonstrate, like all health-care professionals, that they make a significant difference in the lives of children with haemophilia and their families. Research to provide evidence-based care is an essential issue today as well as in the near future. Moreover, the results of treatments are often based on case histories and there are few controlled studies. Furthermore, a distinction has to be made between 80% of the children with haemophilia living in countries with no access to sufficient replacement therapy and those children who have access to primary prophylaxis or at least adequate on-demand treatment in the home situation. For this last group of children emphasis should be on normal motor development and stimulation of physical activities that are normal for their age and social situation.

**References**

TREATMENT OF JOINT PROBLEMS IN CHILDREN


CHAPTER

25

Rehabilitation and physiotherapy for adults with haemophilia

F. Querol and K. Beeton

Introduction

During the 1960s, the introduction of factor concentrates radically changed the lives of people with haemophilia. Prior to then, the life expectancy of a person with haemophilia was only 40 years. The advent of effective treatments offered new hope of a normal life expectancy, but sadly the introduction of the human immunodeficiency virus (HIV) precipitated the early death of many haemophilic patients. Nowadays, the quality of replacement therapy, together with prophylaxis and home treatment programmes, offers a high level of safety and effectiveness so that a haemophilic patient has a life expectancy similar to that of the normal population [1-3].

One of the problems often associated with old age is arthritis, a degenerative process that affects the majority of the adult population. In the haemophilic patient, arthropathy can affect the joints from a very early age and so it is essential that patients with haemophilic arthropathy receive effective rehabilitation [1,4,5].

The development of haemophilic arthropathy is often related to the plasma levels of circulating factor and the effectiveness of factor concentrates. In severe haemophilia, the circulating level of factor VIII and factor IX is less than 1 IU/dL and, without treatment, the haemophilic patient is likely to develop musculoskeletal bleeds from infancy. These bleeds can lead to the development of arthropathy and disability in youth and older age [1]. In order to prevent haemophilic arthropathy and improve the quality of life for the haemophilic patient, prophylactic treatment must be started before joint damage has occurred [6,7].

The aim of prophylaxis is to maintain a level above 1 IU/dL so that the severely haemophilic patient is effectively functioning as a moderately affected patient [8]. However, there are some questions that need to be considered.

- At what age should prophylaxis be started?
- What dosage and circulating factor level are required?
- What dosage is required for the treatment of haemarthrosis?

Despite recent developments, there are many patients worldwide who do not have access to primary prevention and so many patients continue to experience bleeds and to develop haemarthrosis, synovitis, haematoma and arthropathy [9-12]. Patients on prophylaxis can also still experience musculoskeletal bleeds. These musculoskeletal problems can affect function so rehabilitation and physical therapy, as well as effective treatment regimens, are essential. The aim of this chapter is to describe physiotherapy and rehabilitation procedures that can help to improve the quality of life of the haemophilic adult patient.

Aims of rehabilitation in haemophilia

The aims of rehabilitation of the haemophilic patient are to prevent and treat the musculoskeletal problems that cause disability. Rehabilitation after orthopaedic surgery is also required.

The aims of rehabilitation are:

1. diagnosis and treatment of the musculoskeletal system;
2. advice and education regarding physical activities; and
3. collaboration with other members of the multidisciplinary team to improve the overall health of the patient [13].

Management of haemarthrosis before factor replacement was available required a conservative approach. Treatment included immobilization, cold therapy and splinting until the blood had been reabsorbed [14]. Patients often required long stays in hospital, the incidence of rebleeding was frequent which led to joint damage, and arthropathy was inevitable. Aspiration of the joint was not indicated and orthopaedic surgery provided limited treatment options. Physiotherapy aimed to improve the function of the patient but could often not prevent the development of deformities caused by haemophilic arthropathy and the associated disability and handicap.

Factor concentrates have enabled more effective management of bleeding episodes and so hospitalization is less often required. Availability of concentrates has also enabled orthopaedic surgery to be performed to relieve pain and correct deformities as well as facilitated strategies for the prevention and treatment of haemophilic arthropathy [1,4].

Functional evaluation of the locomotor system

Range of movement (ROM), joint circumference and muscle strength are the basic physical assessment procedures used to
Table 25.1 Range of movements: average values.

<table>
<thead>
<tr>
<th></th>
<th>Shoulder</th>
<th>Elbow</th>
<th>Hip</th>
<th>Knee</th>
<th>Ankle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexion</td>
<td>158</td>
<td>146</td>
<td>113</td>
<td>134</td>
<td>18</td>
</tr>
<tr>
<td>Extension</td>
<td>53</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>Abduction</td>
<td>170</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adduction</td>
<td>50</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External rotation</td>
<td>68</td>
<td>71</td>
<td>45</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Internal rotation</td>
<td>68</td>
<td>84</td>
<td>45</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

The Musculoskeletal Committee of the World Federation of Haemophilia developed a system of clinical evaluation, described by Gilbert in 1993 [17]. Recently, Manco-Johnson et al. [16] have proposed a few modifications basically related to the evaluation of gait and pain with or without activity. These protocols are used at present for the clinical evaluation of haemophilic patients.

Physiotherapy for musculoskeletal bleeds

Haemarthrosis

A haemarthrosis is defined as the presence of intra-articular blood as a result of major or minor trauma. In many cases, patients may be unaware of any provoking factor. Without factor concentrates, the blood can expand the joint until it is tense and swollen. At that time the pain is often severe and active movement is impossible.

The diagnosis of a haemarthrosis should evaluate the following:
- Position of the joint.
- Size of the joint by measurement of circumference.
- Local temperature.
- ROM both actively and passively providing no pain is produced.
- Strength of muscles overlying the joint if possible.
- Functional limitations.

Having diagnosed the problem, there are two possibilities for treatment:
- conservative treatment; or
- aspiration.

The guidelines for rehabilitation are summarized in Fig. 25.2. Haemarthroses can be defined as either spontaneous or traumatic, severe (serious bleeding episode) or mild (minor bleeding episode) and, depending on the time scale, as acute, subacute or chronic (Fig. 25.3). Mild bleeds often settle quickly with adequate factor concentrates and modified activities. In severe bleeds the haemarthrosis can provoke an inflammatory response.

Muscle strength is graded as follows (Table 25.2).

5 Normal.
4 Good contraction against resistance.
3 Full available range of movement against gravity.
2 Full range of movement with gravity counterbalanced.
1 Flicker of muscle activity.
0 No muscle contraction.

Table 25.2 Muscular strength: evaluation.

<table>
<thead>
<tr>
<th>Score</th>
<th>Concept</th>
<th>Appropriate physiotherapy techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal strength</td>
<td>Maintenance of good physical condition. Appropriate sports</td>
</tr>
<tr>
<td>4</td>
<td>Good contraction against resistance</td>
<td>Exercises with progressive resistance to increase muscle strength and endurance</td>
</tr>
<tr>
<td>3</td>
<td>Full available range of movement against gravity</td>
<td>Active exercises. Isotonic contractions. Exercises to increase strength and endurance. Hydrotherapy</td>
</tr>
<tr>
<td>2</td>
<td>Full range of movement with gravity counterbalanced</td>
<td>Assisted movements/active mobility with suspension or hydrotherapy</td>
</tr>
<tr>
<td>1</td>
<td>Flicker of muscle activity</td>
<td>Isometric exercises/assisted movements</td>
</tr>
<tr>
<td>0</td>
<td>No muscle contraction</td>
<td>Passive motion to maintain mobility</td>
</tr>
</tbody>
</table>
synovial reaction and invariably requires immobilization, cold therapy and a progressive programme of exercises as well as factor concentrates. In cases of more severe bleeds, the joint may benefit from a splint, which can be static or dynamic, to help control movement and reduce load.

It is essential to undertake a differential diagnosis in order to exclude other causes of pain and swelling (Table 25.3). In particular, patients who are immunosuppressed can develop a septic arthritis. This can present with a tense painful joint which could be mistaken for bleed. Septic arthritis may be associated with fever and rigors, and may be preceded by infections elsewhere or dental interventions. The definitive diagnosis is established by means of aspiration and cytology of the synovial fluid. The suspicion of septic arthritis demands immediate
hospitalization to instigate suitable antibiotic therapy as well as factor concentrates.

Synovitis is caused by the progressive accumulation of iron deposits as a result of repeated extravasation of blood into the joint. An inflammatory response is generated and begins to destroy the joint surfaces [18]. Different physiotherapy modalities can be used including pulsed short-wave diathermy, ultrasound, electrical stimulation, low-frequency magnetic waves and cold therapy to reduce the inflammatory response [1,4,5,15]. The synovitis also provokes muscular atrophy and weakness and this can cause a functional deficit. The muscular atrophy, and its consequences, can be improved with the use of a progressive exercise programme including hydrotherapy and electrical stimulation [19]. If the synovitis does not respond favourably to conservative treatment within 3–6 months it is advisable to consider synoviorthesis or synovectomy followed by a programme of physiotherapy [1,20].

**Haematomas**

Muscle haematomas are the second most common type of bleeding disorder in a haemophilic patient. In the adult patient they are less frequent than in the child, because physical activity of adults is usually more controlled. Haematomas in the adult haemophiliac can be severe and may be associated with bruising (Fig. 25.4).

Bleeding is not usually confined to the muscle and there is often accumulation of blood in the subcutaneous tissues as well. A haematoma can compromise adjacent nerves which can diminish function which then requires additional rehabilitation and physiotherapy [1,4,5,15,21].

If effective treatment with concentrates is not commenced, the haemorrhage continues until the pressure in the connective tissues is equal or exceeds the pressure in the affected vessels. Once bleeding stops, the process of reabsorption is initiated. In the muscles, fibrous tissue can replace contractile tissues so it is important to prevent rebleeding and the encapsulation and formation of cysts. Ultrasonographical examination can be useful to evaluate the bleed and to monitor recovery.

In the acute phase of severe muscle haematomas, besides adequate factor replacement (factor VIII 24–40 IU/kg/12–24 h in haemophilia A and 30–40 IU/kg/24 h in haemophilia B), immobilization is needed in a pain-free position and cold therapy should be applied for 10–15 min 3–4 times a day. After 24–48 h it is important to obtain more functional positions of the affected region to avoid muscular fibrosis in a shortened position. Mobility must be carefully monitored. In the subacute phase, as soon as active movement does not cause pain, isometric contractions can commence, progressing to passive movements and later resistance exercises until normal strength has been restored. Pulsed ultrasound can be useful to absorb the haematoma. Muscle weakness and atrophy can be managed with a progressive exercise programme, electrical stimulation and biofeedback.

<table>
<thead>
<tr>
<th>Table 25.3 Differential diagnoses between haemarthrosis and synovitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemarthrosis</strong></td>
</tr>
<tr>
<td>Chronology of the pain</td>
</tr>
<tr>
<td>Characteristics of the pain</td>
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<tr>
<td>Joint palpation</td>
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<tr>
<td>Joint mobility</td>
</tr>
<tr>
<td>Strength</td>
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<tr>
<td>Therapeutic response</td>
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</table>
Iliopsoas haematomas can be an especially serious problem. Differential diagnosis must be considered as pain in this region can be caused by a haemarthrosis in the hip or even acute appendicitis. Treatment involves rest during the first 24–48 h to reduce the flexion of the hip and to prevent the risk of rebleeding and subsequent haemophilic pseudotumours. Other complications of muscular haematomas are neurological involvement because of compression of peripheral nerves and compartment syndromes. It is always important to be meticulous in the application of any bandages or splints.

**Haemophilic arthropathy**

Haemophilic arthropathy is joint destruction with similar characteristics to rheumatoid arthritis and degenerative arthrosis, although the cause is clearly identified as a result of recurrent bleeds. The clinical manifestations of haemophilic arthropathy are pain, loss of range of movement and functional limitation, which leads to disability. Physiotherapy and rehabilitation are very important in both preventing and managing arthropathy [1,4,5,15,22]. The prevention of haemophilic arthropathy is a fundamental aim of factor concentrates. Haematological treatment must be combined with a programme of physiotherapy to maintain and support a good physical status for activities of daily life including appropriate sports.

The pain and inflammation of haemophilic arthropathy can be managed with non-steroidal anti-inflammatory drugs (NSAIDs), and also with medications that modify the joint structure such as glucosamine sulphate [23]. Any medication should be combined with appropriate physiotherapy.

Electrotherapy can be a useful adjunct to exercises [24]. Orthotics can also be beneficial in relieving pain. The surgical treatment of haemophilic arthropathy is always associated with rehabilitation postoperatively [25].

**Specific rehabilitation of the joints in the haemophilic adult patient**

**Rehabilitation of the shoulder**

Haemarthroses require immobilization in a functional position with a sling, as well as an appropriate factor regimen. Cold therapy should be applied 2–3 times a day. As the acute symptoms subside, pendular exercises are initiated (Fig. 25.5) followed by active exercises and then exercises against resistance. Hydrotherapy can be useful to restore shoulder function. The physiotherapist must monitor joint mobility and muscle power avoiding deltoid atrophy.

If pain is severe then transcutaneous electrical nerve stimulation (TENS) can be helpful in relieving pain and reducing inflammation so improving mobility. Pulsed ultrasound can also be useful for haematomas and tendinitis.

**Rehabilitation of the elbow**

In the upper limbs, the elbow is the joint that is most frequently affected by bleeds. An acute haemarthrosis must be immobilized in an antalgic (pain-free) posture generally involving flexion of the elbow with slight supination. After the first 24–48 h the elbow can be mobilized, although range of movement may initially not be full and a splint may be used in a functional position, 90° of flexion and a neutral position of prosupination. The treatment programme follows the standard guidelines. It begins with isometric exercises (contraction without movement)
Rehabilitation of the hip

It is important to differentiate haemarthrosis of the hip from an iliopsoas haematoma. Symptoms from a haemarthrosis usually include pain and limitation of all ranges of movement whereas haematoma of the iliopsoas causes limitation of flexion–extension, but rotation, distraction and approximation of the hip can be pain-free.

The management of a haemarthrosis consists of immobilization followed by progressive mobilization and gait re-education as pain allows. A walking frame or crutches may be required to reduce weight-bearing. Cold therapy has minimal effects on a haemarthrosis of the hip because of the depth of the joint. An iliopsoas haematoma demands absolute rest and sometimes traction is needed (Fig. 25.6). Hip flexion deformities must be prevented in the long term and so posture re-education followed by progressive exercises for mobility and strength and gait re-education must be continued until full range of movement and muscle strength have been achieved.

Rehabilitation of the knee

The knee is one of the joints most prone to bleeding. The knee is a relatively unprotected joint with an extensive synovial membrane full of blood vessels and continually under great biomechanical stress.

The management of a knee haemarthrosis includes factor concentrates, immobilization in a pain-free posture as with all the joints, followed by cold therapy. As pain improves the knee is supported in extension of 0° and isometric exercises are begun. As function improves proprioceptive training, muscle strengthening and gait re-education are added to the programme. It is important to ensure that there is sufficient muscle control to prevent any instability of the knee. If there is any muscle weakness splints may be required. Hydrotherapy and exercises in a swimming pool are an excellent method for facilitating functional recovery of the knee. Synovitis of the knee is often associated with severe muscle atrophy. Arthropathy of the knee, depending on severity, needs different methods of physical therapy but always with the same aims; to relieve pain, to improve strength and to improve or to maintain mobility of the joint.

Rehabilitation of the ankle

The ankle is the first joint that supports the load of the body and is submitted to constant stress, especially in sporting activities. During the weight-bearing phase of gait from heel strike to push off, microinjuries can occur which can lead to haemarthroses. In order to prevent haemarthroses, the use of insoles and special shoes are recommended as they can help to reduce the load on the ankle joint [26]. As with other joints, once the acute phase of the bleeding episode has settled, it is important to maintain prophylaxis in order to prevent re-bleeding.

The rehabilitation of the acute phase has the same approach as in other joints, first immobilization in pain-free posture, generally plantar flexion and plantar inversion. After 24–48 h it is usually possible to place the ankle in a neutral position of dorsiflexion–plantarflexion and eversion–inversion. The use of thermoplastic splints facilitates appropriate positioning during different phases of the problem. Crutches may be required to reduce loading on the joint. As pain settles, mobility and strengthening exercises can be commenced. Cold therapy and alternating hot–cold baths are helpful to reduce swelling. Interferential currents and other electrotherapy techniques can also relieve pain and improve swelling.

If ligamentous injuries are suspected, ultrasonography can be used to evaluate the presence or absence of a joint effusion. If severe, the joint may require immobilization and later support provided with orthotics or elasticated supports. Gradual loading is introduced as recovery continues.

Postsurgical rehabilitation

Currently, most orthopaedic surgery for patients with haemophilia is carried out for the management of arthropathy. Recent research on young haemophilic adults in Spain and France shows clinical–radiological changes in more than 80% [27,28]. These data do not differ greatly from the study performed in 1978 [29] where 99% of severe Spanish haemophiles presented with arthropathy. Considering that the life expectancy of a haemophilic patient is now similar to that of the normal population, this suggests that there will be a need to continue using surgical technologies. In particular, synovectomy, tendon...
release, capsulotomy, osteotomy and total joint arthroplasty are commonly used [1,25]. Total joint arthroplasties of knees and hips can improve quality of life by relieving pain and improving mobility. Recently, beneficial results have also been identified with the use intra-articular hyaluronic acid [30,31]. This may be indicated for patients who have pain but who do not yet require arthroplasty.

**Orthotics**

Orthotics includes any external device to correct or support a joint. This can include prevention of deformity, correction of biomechanics of the lower limb or immobilization of a joint.

In the haemophilic patient the principal injuries that provoke disabilities and which need orthotic support affect the lower limb, the foot and ankle and the knee and, in the upper limb, the elbow. In the foot, the use of orthopaedic footwear or insoles can help to improve gait by reducing strain on joints both locally and further up the kinetic chain as well as reducing the impact of heel strike. For those patients who have inhibitors so the use of factor concentrates has limited effect, or in patients who have ‘target’ joints and have repeated bleeding in lower limb joints, load-relieving orthotics, as well as crutches, can reduce the stress on affected joints. Finally, silicone cushions, knee pads and ankle supports can be useful to provide additional protection for activities and sports as well as providing support for joints with arthropathy.

**Sports**

Physical activity and sport are a fundamental component in the management of a patient with haemophilia. Activity is important from both physical and psychosocial aspects [32–34]. Exercise improves physical condition and mental health, but in the haemophilic patient it is particularly important to consider safety factors as it is important to prevent injuries.

The haemophilic adult patient may be restricted in the sporting activities that he can pursue. The prevalence of arthropathy in the haemophilic adult patient can be high and the presence of arthropathy will limit the sports which can be undertaken. In the census of haemophilic patients controlled by Unidad de Coagulopatias Congénitas de Valencia (Spain) no patient was practising sport on a regular basis.

Gilbert et al. [34] classified sports under three categories. Later, Heijnen et al. [35], in an interesting study on sport and haemophilia, suggested that sports should have the same acceptance in different countries. There are the so-called ‘advisable’ sports, that is to say, those sports which can be performed safely as the amount of effort is minimal. In the second category are sports which have an ‘acceptable’ risk if practised with suitable protective equipment (specific footwear, knee pads, elbow supports, etc.). This enables the physical, social and psychological benefits of sport without undue risk. Thirdly, there are dangerous sports, which present a high risk of injuries even in the normal population.

Table 25.4 summarizes two categories: advisable sports and dangerous sports. Patients should be advised on suitable sports based on their motivation and personal preferences, problems with joints and incidence of re-bleeding, previous training, previous sports experience, friends’ and relatives’ attitudes and also the occurrence of injuries during or after the practice of the sport. Involvement in sport at a competitive level needs to be undertaken with great caution and following advice and consultation with all members of the multidisciplinary team.

Swimming is recommended as one of the best forms of exercise for patients with haemophilia. However, finding a suitable pool close to home or place of work with easy accessibility is often not easy. Walking can be an appropriate form of exercise, provided that the lower limb joints are not markedly affected by arthropathy. Jogging can be recommended if the physical condition of the patient allows it and suitable footwear is used.

**Conclusions**

The availability of prophylaxis and home treatment programmes has improved the lives of people with haemophilia immeasurably. Being able to control bleeding has improved life expectancy and reduced the severity of musculoskeletal bleeds. In spite of this, patients who did not have access to concentrates early in life may develop joint arthropathy and younger patients, even those on prophylaxis and regular treatment from an early age, may still experience bleeds affecting the musculoskeletal system. The importance of physiotherapy for these patients cannot be underestimated both in the treatment and prevention of musculoskeletal problems.

**References**


**Table 25.4** Recommended and dangerous sports for the haemophilic patient.

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CHAPTER

26

Rehabilitation following ankle surgery in haemophilia

B.M. Buzzard and P.J. Briggs

Introduction

The tibiotalar, or ankle joint is frequently affected in haemophilia, in contrast to the subtalar joint which is involved much less frequently. The ankle is reported to be the third most frequently affected joint after the knee and the elbow, accounting for 14% of all joint bleeds [1]. Ankle joint haemorrhages appear to occur at an early age, being the most frequent lower limb joint to be affected in the second decade of life, with the knee joint being particularly affected in the third and fourth decades [2].

The effect of repeated joint haemorrhages, causing synovitis and cartilage damage, is progressive joint destruction. Although 20% of patients will have a slight impairment of their ability to work or attend school in the 11–20-year age group as a consequence of their ankles, 80% will have some difficulty by the age of 40, with 40% moderately or severely affected [3]. Patients experience pain, stiffness, deformity and muscle wasting. The impairment of ankle function makes the joint more prone to further bleeds. The alteration of lower limb biomechanics because of pain and stiffness in the ankle joint may increase the strain on other joints during walking, increasing the risk of damage to these also. We can speculate that impairment of the ankle may contribute to the rising incidence of knee joint bleeds in the twenties and thirties.

Assessment

Prior to any treatment, a full musculoskeletal assessment should be carried out including subjective and objective parameters. When considering patients with ankle disorders it is important to assess other foot and other lower limb joints and to observe the patient standing and walking. Foot and ankle deformity may be seen. Tenderness and warmth of the joint may indicate inflammation. Range of motion in the ankle, subtalar and midtarsal joints are measured. Weight-bearing radiographs of the ankle and hind foot joints are essential before considering surgery. Magnetic resonance imaging (MRI) scans may be helpful in assessing early joint disease. Having accurate baseline data is essential for documenting change in function and the effects of treatment.

Patients with haemophilic arthropathy affecting the lower limb joints are often young and are likely to require long-term supervision and management. Holistic care, considering impairment, disability and handicap as defined by the World Health Organization (WHO), is important [4]. The WHO has more recently revised this concept which defines a ‘three-dimensional’ description of an individual’s functional health status including:

1 body function and shape;
2 activity; and
3 participation [5].

Functional ability can be assessed by patient interview and observation and by direct physical testing. Various scores such as the International Classification of Impairment, Disabilities and Handicaps (ICIDH-2), Arthritis Impact Measurement Score (AIMS-2), SF36 and Quality of Life Measures can be used [6–8]. However, the reliability of these scores remains uncertain and is the subject of current debate [9].

Physiotherapy and ankle protection

It is clearly important to control the bleeding tendency. Joints that show a tendency to repeated bleeds may be improved by physiotherapy and protective measures. Splinting and ice are important in promoting speedy resolution of acute episodes. Restoration of joint motion and then strength are important in maintaining normal joint function and lower limb biomechanics [10]. Specific measures to protect the ankle include splints, shock-absorbing pads and boots. The Aircast® ankle splint has been shown to reduce the frequency of bleeds in young children [11]. This provides physical protection against direct injury from knocks and blows, as well as reducing the tendency to indirect injury from twisting, while allowing flexion–extension movement. The usefulness of shock-absorbing pads remains uncertain. Silicone heel pads have been shown to reduce the incidence of ankle bleeds and ankle pain in one-third of patients [12], but biomechanical studies suggest that they lead to an
alteration in the normal ankle mechanics, characterized by uncontrolled changes in ankle motion and increased angular velocities, which arguably may lead to a higher probability of joint bleeds [13]. Boots are capable of reducing ankle and subtalar motion and reducing bleeding tendency [2]. The reduced movement of the foot will affect the mechanics of the knee and hip during gait and care in the design of the boot and the sole is important. Compliance, particularly in the younger patient and girls with bleeding disorders, is likely to be a problem.

**Surgery for the ankle in haemophilia**

If non-operative measures fail to control symptoms and bleeds, then invasive measures may be considered. However, this should not be viewed as failure, as there may be advantages in timely surgery at a stage when the function of the ankle can be restored. Ten years ago ankle arthrodesis was the only surgical procedure considered useful in the management of the ankle joint affected by haemophilia. This should be regarded as a salvage procedure for a joint destroyed by the arthritic process that is causing pain, deformity and disability. In recent years other surgical procedures have been used, such as synovectomy, osteotomy and cheilectomy, with the aim of controlling the bleeding tendency and restoring function in the ankle joint.

The question of surgery cannot, unfortunately, be considered without addressing the issue of the human immunodeficiency virus (HIV). The major effect of this is to increase the postoperative infection risk, especially in patients with low CD4 lymphocyte counts. This is of particular concern in those undergoing implant surgery such as joint replacement. There has been concern that surgery may accelerate the development of the acquired immunodeficiency syndrome (AIDS) but this does not appear to occur in elective joint surgery in haemophilic patients [14].

**Synovectomy**

Chemical and radioactive methods of synovectomy are used in the control of joints affected by recurrent bleeds. Rifampicin and yttrium-90 have both been shown to be effective [15]. Rifampicin injections can be painful and repeated injections are usually required. Yttrium-90 is expensive and less readily available. Surgical synovectomy is an effective alternative. Open or arthroscopic synovectomy of the ankle can dramatically reduce the incidence of bleeds and, in contrast to other joints such as the knee, postoperative rehabilitation is relatively easy [16]. The arthroscopic method allows better access to the posterior aspect of the ankle, but clearance of the synovium from the anterior part of the joint, achievable by the open technique, appears to be sufficient. Reduction of the number of bleeds into the joint should reduce the trend toward joint destruction and arthritis. It will be more effective in joints where there is no, or, at most, minimal cartilage damage.

Rehabilitation following synovectomy is relatively simple whichever technique is used. Factor replacement will usually be required. Some of these procedures can be painful and adequate analgesia should be provided. Physiotherapy aims to reduce pain, regain movement and mobility, and restore function. Ice therapy in conjunction with elevation of the limb for the first 24 h is recommended with or without compression, depending on the amount of swelling. Active range of motion exercises are commenced within the first 24 h. Weight-bearing usually starts at 24–48 h and hospital discharge can take place once the patient is safe from the haematological point of view and mobile. Physiotherapy review or follow-up is again dependent upon the active range of motion obtained, degree of swelling and mobility level. Short-term outcomes are favourable following the procedure [16].

**Deformity correction**

Deformity will affect the mechanics of the ankle and lower limb. However, there is little evidence to show that varus or valgus deformities of the tibia above the ankle will lead to the development of osteoarthritis in the non-haemophilic patient [17]. Valgus alignment of the ankle joint may develop in haemophilia, thought to be a consequence of overgrowth of the tibia because of the inflammatory reaction after repeated bleeds. Pearce et al. [18] showed that correction of this deformity by supramalleolar osteotomy can reduce the number of bleeding events and improve pain relief. However, the deformity is rarely marked and is probably not appropriate in the majority of haemophilic ankles.

Patients can be troubled with deformities unrelated to their haemophilia and consideration should be given to managing these. A cavus deformity can cause hind foot instability because of the supinated posture of the heel during the stance phase of gait. A flat foot causes increased tension on the medial structures of the ankle and hind foot [19], although there appears to be little change in the centre of load and joint pressure distribution in the ankle and subtalar joints [20]. In a patient suffering repeated ankle bleeds with a coexistent foot deformity it is logical to try and manage this in the hope of protecting the ankle. In principle, this will either mean control with orthoses and footwear modifications, or correction with surgery. Management of deformity can reduce symptoms, improve function and protect the ankle as well as other lower limb joints.

**Cheilectomy**

Osteophytes, or spurs, may be seen on radiographs of the ankle. Whether these are the result of the inflammatory reaction after repeated haemorrhages or part of the progression of the joint
degeneration is uncertain but they do appear to occur early in the haemophilic arthritic process. They are commonly seen at the anterior aspect of the ankle arising from the tibial articular margin and as they develop they can give rise to pain and restriction of movement. Pain on ankle dorsiflexion and catching or clicking-type symptoms are characteristic. Removal of the osteophytes (cheilectomy) reduces pain and improves movement in the ankle. In a small series of six patients with seven symptomatic ankles pain was markedly reduced, dorsiflexion increased 5–10° and, interestingly, plantarflexion increased 5–25° [21]. Walking tolerance increased and psychological parameters improved. Calf pain commonly occurs in the postoperative rehabilitation period and may be caused by unaccustomed stretching of the calf musculature. It is anticipated that the best results would be obtained in joints otherwise reasonably well preserved with maintenance of the joint space, but surprisingly good results have been obtained on occasion when there has been complete loss of articular cartilage. Recurrence of osteophytes occurs, but many patients gain several years' relief of pain and improvement of function.

The results in patients treated in Newcastle upon Tyne are presented in Table 26.1. There were eight treated ankles in seven patients, one patient dying of an HIV-related illness. Their age at operation was 12–49 years and the mean hospital stay was 4 days following surgery. Follow-up was from 2 months to 10 years.

The aim of physiotherapy is again to reduce pain, and improve movement and function, and this should start on day 1 following factor replacement. Ice therapy using conventional ice packs or Cryocuff®, which combines ice and compression, can be an effective means of reducing pain and postoperative swelling, although this tends to be minimal following cheilectomy. Early active range of motion exercises to improve dorsiflexion–plantarflexion and pronation–supination are encouraged within the first 24 h. Weight-bearing can commence after 24 h, within the limits of discomfort, using appropriate walking aids if necessary, followed by early discharge from hospital. All patients should receive outpatient physiotherapy, which concentrates upon gait re-education, proprioception and muscle imbalance retraining to allow the patient to obtain maximum benefit from the orthopaedic intervention.

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**Table 26.1 Pre-and postoperative features of patients undergoing anterior cheilectomy of the ankle joint for haemophilic arthropathy. Results in patients treated in Newcastle upon Tyne, UK.**

**Case study**

A 29-year-old male with severe factor IX deficiency, Cl%, HIV-negative and HCV-positive (hepatitis C virus with 1% of Factor IX), had suffered repeated bleeds in his right ankle, usually associated with trauma, since childhood. In recent years he had received prophylactic replacement therapy and physiotherapy management, using ice electrotherapy, exercises programmes and orthoses, all of which alleviated symptoms to a certain degree. He worked as a joiner, which involved a lot of walking, standing and climbing, which aggravated his ankle causing anterior pain and swelling. His symptoms were affecting his ability to continue his job.

Examination showed that the foot and ankle were of normal shape. He was tender on palpation across the front of the ankle joint. He had good flexion–extension range of motion with 10° dorsiflexion and 30° plantarflexion with pain at the limits of motion. There was crepitus, particularly on the lateral aspect. Subtalar movements were unaffected and pain-free. X-rays showed haemophilic arthropathy with both distal tibial osteophytes and talar osteophytes.

Surgery under factor IX control was performed without complication, and the patient was commenced immediately with active range of motion exercises, achieving plantigrade within the first 24 h. He was mobilized, full weight-bearing the following day and discharged from hospital 2 days later. He attended outpatient physiotherapy twice a week in order to continue muscle strengthening, proprioceptive training and gait re-education. Four weeks postoperatively he had no pain, no swelling, with an active range of motion of 20° dorsiflexion and 40° plantarflexion (Figs 26.1 and 26.2). He returned to work 4 weeks later and recommenced recreational activities. Four years following surgery he had maintained range of motion, was pain-free and has had no further bleeding episodes into this joint.

**Restoration of function**

Most patients who have suffered from repeated ankle joint haemorrhages have abnormal gait patterns with resultant muscle imbalance, movement dysfunction and a decrease in
REHABILITATION FOLLOWING ANKLE SURGERY

Fig. 26.1 (a) Preoperative lateral and (b) anteroposterior radiographs of the ankle in a patient with haemophilic arthropathy.

Fig. 26.2 (a) Postoperative lateral and (b) anteroposterior radiographs of the same ankle following anterior cheilectomy.

Proprioceptive responses [22]. Recovery from the surgical procedure may be relatively straightforward, but the rehabilitation programme can be long and intensive. Muscle imbalance rehabilitation focuses on four main strategies [23].

1 Control of the neutral joint.
2 Control of movement.
3 Control through range of movement.
4 Regaining muscle length or extensibility.

A gradual exercise programme, predetermined by the physiotherapist, will help to restore muscle balance thus reducing further stresses and strains upon the joint.

Linked to restoration of muscle balance is proprioceptive training, particularly important at the ankle joint where instability can be a problem. Proprioception can be defined as the receipt of information from muscles and tendons that enables the central nervous system to determine movements and position.
of the body and its parts in space. Proprioception (sense of position) and kinaesthesia (sense of movement) work closely together to enable coordinated quick controlled movement, balance and stability.

The basis of rehabilitation is dependent upon a balanced relationship between the central nervous system and the musculoskeletal system [24]. A detailed programme of proprioceptive exercises should be incorporated into the rehabilitation process under the supervision of a physiotherapist following any ankle joint event, including haemorrhage, injury or surgery. Exercises developed for rehabilitation of the ankle include the following.

- Standing on one leg and holding position for 1 min.
- Standing on one leg, eyes closed, hold for 1 min.
- Walk around the edge of a mat slowly clockwise five times and then anticlockwise five times. Foot should be half on half off the edge of the mat.
- Stand on one leg, throw a ball against a wall with one hand and catch with the other.
- Stand on one leg, go up on toes for 30 s. Repeat five times.
- Wearing socks on a smooth floor. Keep feet together. Shuffle sideways using toes and heels to pivot (Shimmee). Go 2 m in one direction and then 2 m in the other direction.
- Balance board exercises.
- Trampoline exercises.

There is a gradual progression and intensity of these exercises, which should be carefully supervised by the physiotherapist, taking into consideration other affected joints. Programmes should be individually tailored to the patient.

**Arthrodesis**

Arthrodesis is the mainstay for surgical management of the ankle destroyed by the haemophilic process. Reduction of pain and bleeding events, correction of deformity and improved walking ability can be achieved [2,25-27]. Current techniques, including open and arthroscopic methods, have a high fusion rate [28-30] and arthrodesis is well tolerated with many patients regaining a good level of functional ability. Patients often require this at a relatively young age in their twenties and thirties.

Physiotherapy following joint arthrodesis consists of advice regarding elevation of extremity in the early days and maintenance exercises for the limbs. Patients will usually be immobilized in plaster for 2-3 months, and the surgeon will usually recommend a period of non-weight-bearing, depending on the strength and rigidity of any fixation used in the arthrodesis. Specific exercises for mobility of the hip and knee should therefore be taught.

Instruction in the use of ambulatory aids will be required until union has occurred. Once the patient is out of plaster, rehabilitation will again focus on gait re-education, improving muscle strength and proprioceptive training. Restoration of function in the ankle will clearly not be possible after arthrodesis, but other joints such as the subtalar and midtarsal that were immobilized in the plaster, will require attention. Arthrodesis will necessarily affect the function of other joints, including the knee. Shoe adaptations such as rocker soles or splints, may be helpful in minimizing these effects.

**Joint replacement**

Although good results are obtained with arthrodesis, this is at the expense of loss of motion at the ankle. Ankle replacement has historically not been found to be a reliable procedure for the management of arthritis [31], but newer designs appear to be achieving better results [32,33]. There are no published results of the use of ankle replacement in haemophilic arthritis apart from a single case report where the outcome was poor [26]. The fact that patients present with arthritic problems at a relatively young age raises concerns about the durability of joint replacement and the potential need for revision surgery. It is difficult to make objective clinical comparisons between arthrodesis and joint replacement in the ankle, but it is probable that if the subtalar and midtarsal joints are functioning normally then an arthrodesis will provide a good durable outcome. The development of secondary arthritic changes in these joints after ankle arthrodesis is probably related to pre-existing changes rather than the effect of the arthrodesis [28,30]. In contrast, if patients already have significant arthritic change and stiffness in the subtalar and midtarsal joints then preservation of some flexibility at the ankle level may be advantageous.

Knee replacement surgery provides good results in haemophilic arthritis [34-36], but the complication rate is higher than one would expect for other forms of arthritis and some series report relatively poor results [37,38]. Aseptic loosening and infection are the most frequent concerns. The reasons for this are uncertain but may be related to poor bone quality, recurrent bleeds and relative youth of the patients leading to early joint replacement failure. Whether these concerns are applicable to the ankle is unknown. Given that there is still some uncertainty of the results of ankle replacement in other forms of arthritis it is understandable that surgeons are cautious in applying this to patients with haemophilic arthritis.

**Conclusions**

In conclusion, the ankle is commonly affected by haemophilia and at a relatively young age. Disease control, physiotherapy and joint protection measures are important in preventing long-term damage to the joint and maintaining function. Arthrodesis remains the salvage procedure of choice in the joint destroyed by the arthritic process, but recent years have seen the establishment of alternative surgical procedures such as synovectomy, deformity correction and cheilectomy in restoring ankle function and reducing the incidence of bleeds. These procedures, performed at an early stage, may slow the progression of joint damage reducing the need for salvage procedures.
Joint replacement may become a practical proposition but few centres will have more than a few patients where this might be considered. A multicentre study collecting patients from a number of centres is the only way that meaningful information will be obtained.

References

6 Miscellaneous
CHAPTER 27

Motion analysis in children with haemophilia

A. Seuser, T. Wallny, G. Schumpe, H.H. Brackmann and C. Kramer

Introduction

The main location of bleeding in subjects with haemophilia is the locomotor system. Haemophilia-related arthropathy progresses much quicker than normal arthritis. The development of a so-called target joint is highly likely in subjects with suboptimal substitution of coagulation factors. The joints involved are the knee, ankle and elbow. Factors such as abnormal morphology, necessary surgical procedures, radiodiagnostics and conservative treatment have always attracted scientific study in haemophilia [1-4]. However, little research has been done on the functional performance of the haemophilic joint and no studies are available on joint performance in the growing body and how it is affected by a chronic disease such as haemophilia. We know from biomechanical motion analyses in healthy adults and subjects with arthritis that the locomotor system is highly susceptible to external influences. Minor changes in function may produce major joint stress which is not amenable to study by clinical or radiological examination.

Analysis of the biomechanism of human locomotion is the basis for understanding the principles of normal and pathological performance for all human joints. Many parameters may be used for describing the biomechanics of human motion, but some are more important than others in presenting the complex factors involved. These include relative joint angles, angular velocity, angular acceleration and, for the knee joint in particular, the measurement and interpretation of the roll and glide mechanism. All these parameters will help us establish the correlation between joint load and functional performance [5-9].

Movement via the locomotor system is the product of a balanced interaction of external and internal forces. External forces comprise gravity, friction and ground reaction forces. Internal forces are produced by contraction of muscles, passive extension of connective tissue structures, and contact between the cartilage surfaces of joint bones. This sensitive equilibrium between internal and external forces should be maintained while walking or exercising or any other activities of daily living.

Many studies in adult haemophiliacs and adult healthy subjects have helped us to explain joint function and assess the influence of external factors on the joint. These studies have resulted in the establishment of muscle-strengthening exercises for joint protection, improvement of conservative treatment options, and a lower frequency of bleeds without increasing the use of coagulation factors.

A generation of haemophiliacs with no bleeding-related impairment of the locomotor system has grown up in Germany over the past two decades. This happy circumstance is the result of preventive treatment of the underlying bleeding disorder and immediate curative treatment of any bleeds on the basis of ready access to sufficient quantities of coagulation factor concentrates. With no restrictions on their freedom of movement, young haemophiliacs of this generation feel free to exercise and take part in activities that in the past would have been totally inconceivable. They use this freedom to perform sporting activities and engage in other physical pursuits which on the one hand have the welcome effect of strengthening their muscles, but on the other hand may provoke bleeds out of ignorance about locomotor processes and a lack of awareness of the risks involved.

The lack of understanding of the biomechanics of locomotion in haemophilia has particular implications for the young population. The options for counselling and advising these youngsters are limited. The major objective of ensuring that youngsters receive adequate factor substitution and achieve optimal joint support during their growing years, and the goal of sparing them the restrictions of the generation before them, prompted us to include haemophiliac children in motion analysis studies [10-20]. The first step on the way to achieving this goal was a study involving 13 haemophiliac children aged 4-16 years and 13 healthy children aged 4-16 years.

Materials and methods

Thirteen haemophiliac children and 13 healthy children underwent a motion analysis study. The children were aged 4-16 years, with one child from each age group. The children were similar in terms of their sporting activities. None of the healthy children or haemophiliac children had any symptoms involving the joints of the lower extremities during the study. The haemophiliac children in particular had no radiological or clinical signs of joint damage. There was no record of bleeding involving any of the joints.
Online motion analyses were performed using an Original Ultrasound Topometer (UST, Bonn, Germany). This system measures the time it takes for an ultrasound impulse to travel from a transmitter to four receivers, which are fixed in a frame. Up to 10 transmitters may be used for concurrent measurements. A computer uses the four conduction times that each ultrasound impulse needs to travel from a transmitter to the four receivers at a given ultrasound speed as a basis for tracing the precise three-dimensional location of the ultrasound transmitter. The readings obtained are accurate to < 1 mm.

The small ultrasound transmitters are applied at anatomically relevant points of the body. We use two or three transmitters above and below the joint for joint analyses. The paediatric study was conducted using the knee joint only. To rule out the effects of muscular movement, the transmitters are attached to bony parts of the skeleton or fixed with tight bandages on the thigh.

The readings are processed by a software program we developed ourselves. The three-dimensional spatial data are used to compute relative joint angle, joint angular velocity and angular acceleration in all three dimensions. For knee joints, the program can also compute the roll and glide mechanism of the knee in relation to the flexor–extensor angle. The children underwent three different procedures: treadmill walking, knee bends and measurement of balance on a Posturomed.

**Treadmill walking**

Treadmill measurements were performed after the children had familiarized themselves with the treadmill (Fig. 27.1a). The analysis produced a measuring table showing the knee from the side and from behind during motion (Fig. 27.1b). Shown from top to bottom are:

1. the femoral and tibial angle against a separate point of reference;
2. the knee angle;
3. knee angular velocity; and
4. knee angular acceleration from the side (left) and from behind (right).

**Knee bends**

The children were told what to do and then allowed to perform the knee bends at their own pace (Fig. 27.2a). Knee bend analysis was performed on the basis of the following data (Fig. 27.2b). Motion was viewed from the side and from behind. The measuring table shows, from top to bottom, absolute change in angle of the femur and tibia, relative changes in angle between the femur and tibia (knee angle) and relative angular acceleration between femur and tibia. The bottom part of the measuring table shows determination of the roll and glide profile of the knee joint measured.

![Femoral and tibial motion during walking on a treadmill](image)

**Fig. 27.1** Femoral and tibial motion during walking on a treadmill.
Measurement of balance on a Posturomed

Balance measurement was performed as a basis for correct interpretation of changes in the internal kinematics of the knee joints in the treadmill or knee bend tests and to distinguish them from co-ordination disorders brought about by other factors. The child's shoulder was marked by applying a transmitter to the right and left shoulder. The child was then asked to get up on the Posturomed (manufacturer: Haider Bioswing). This device comprises an unstable platform that moves in two dimensions. Two readings were performed with the child standing on one leg, first the left and then the right (Fig. 27.3a). They had to keep the platform as steady as they could for a period of 10 s.

The parameters analysed were angle changes and positional changes of the various points as viewed from behind and above (Fig. 27.3b). Specifically, the shoulder angle in lateral inclination and in rotation and the angular acceleration were observed. We also analysed the motion of the individual points and their acceleration in all three dimensions.

Evaluation of the various analyses of motion

Treadmill walking

Femoral and tibial angle

The femoral angle was reviewed to establish whether it was rhythmic and sinusoidal, both qualitatively and quantitatively. This applies both in terms of the lateral view and lateral movement of the femur viewed from behind. Loss of sinusoidal curvature, sudden change of direction, fluctuations in angle level and plateau phases qualified as abnormal in both dimensions. The same criteria apply in respect of the tibial angle.

Knee angle

Analysis was essentially as described for the femur and tibia. Swing and stance phase ratios were also reviewed. Usually, the knee follows a defined rhythm in a locomotive subject. The knee touches down in an almost fully extended position, flexion of 10–15° occurs, then the knee joint extends again until almost fully extended, followed by transition to the swing phase (40–50°). The swing phase is made up of initial flexion followed by
extension until heel strike and the next stance phase. Curvature is assessed according to the same criteria as the other angles measured (see Femoral and tibial angle section above).

Angular velocity
Angular velocity in the stance phase in the direction of extension and flexion was analysed. Angular velocity should be approximately equal in both directions. The same applies to flexion and extension in the swing phase. Loss of sinusoidal curvature and rhythm qualifies as abnormal.

Angular acceleration
Basiclly the same applies as described above for angular velocity. Acceleration during flexion and extension in the stance phase and during flexion and extension in the swing phase should proceed symmetrically in the direction of flexion and extension, with no sudden accelerations, with a sinusoidal curve and with no peaks.

Knee bends
The femoral angle during flexion and extension, the tibial angle in flexed and extended position, and lateral deviation of the two angles were presented. Sinusoidal curvature qualifies as normal, as with the treadmill test. The entire process should proceed rhythmically and symmetrically.

The knee angle is analysed from the side and from behind while the subject performs knee bends. The criteria for analysis are as described in the previous section.

Angular acceleration
A rhythmic process as viewed both from the side and from behind is indicative of good muscle control and a physiologically normal joint.

The roll and glide pattern reflects internal knee kinematics
This is the main benchmark for physiological knee joint motion.
We know that knee motion comprises two main movements: rolling and gliding. During the roll the weight-bearing surface switches between the tibia and femur. During the glide, the weight borne by one of the partner joints remains constant. The difference between the two forms of movement is the tilting of the tibia in three dimensions that makes rolling possible.

Software computation can visualize this three-dimensional tilting of the tibia on the basis of a tibial tangential angle. This tibial tangential angle is plotted on a graph in relation to the knee bend angle. The ideal profile of a roll and glide curve plotted on a graph is a line proceeding from the lower left and rising to the upper right. This line corresponds to a normal roll and glide profile. An unchanging tibial tangential angle is indicative of excessive gliding. Excessive gliding denotes excessive sagittal forces and has a detrimental effect on cartilage structures as far as joint load is concerned. In addition to rolling and gliding, the consistency of the curvatures measured between knee bends is also analysed. As with all other motion-testing criteria, rhythm and variation are major factors.

**Balance test using a Posturomed**

**Shoulder angle**

Movement patterns were assessed over 10 s standing on one leg on an unstable platform. Measurements included shoulder angle, angular velocity, angular acceleration, movement of the relevant points, velocity and acceleration in all three dimensions. Benchmarks of normal response were symmetrical deviation of the shoulder–pelvic angle with no major asymmetries or peaks of velocity or acceleration, and a sinusoidal and consistent pattern of movement in all three dimensions.

**Results**

As expected, the results of the test displayed great heterogeneity. Gait variations tended to decrease with increasing age. In other words, the younger the children, the greater the inter-individual variation. Consistency between individual steps was lower. Nevertheless, disturbance of sinusoidal pattern was more frequently seen in the haemophilic children than in the healthy children. Similarly, variations in the stance phase were much less frequent in the healthy children. This includes movement patterns such as transition from the stance phase to the swing phase from a more acute knee flexion angle with loss of terminal extension in the stance phase.

Basically, the same applies in respect of the knee bend test. Surprisingly, the youngest children showed less lateral deviation of the femur and tibia when doing knee bends. This was because of a difference in the technique employed. The youngest children instinctively hunkered down with their feet flat on the floor and thus had better support than the older children who hunkered down on tiptoe. We had not given the children any instructions in this regard.

Analysis of roll and glide patterns shows more precisely than analysis of knee angle that younger children—whether healthy or haemophilic—display greater variation in terms of internal knee kinematics. Although the roll element is dominant, as expected, glide phases are also present and there is a greater discrepancy between flexion and extension. These differences become less apparent as the children grow older and develop a normal adult roll and glide pattern.

Balance is the most heterogeneous element in the series of experiments performed, as it involves the highly sensitive aspect of co-ordination in addition to normal development. Most of the children had never been called upon to perform such a complex co-ordination task. This made it all the easier to differentiate between well-co-ordinated children and less well-co-ordinated children at this point in time.

The study was not designed to produce statistically significant data. This will be the task of a scheduled follow-up study which will include 90 children with haemophilia who will be examined according to the same criteria. Nevertheless, it is possible to draw conclusions on a case-by-case basis, as will be shown in the following.

**Case study**

We wish to compare and contrast the results of a 12-year-old boy with haemophilia with those of a healthy 12-year-old boy. Neither boy reported symptoms involving the hip, knee or ankle joint. The 12-year-old haemophilic and his parents said he had never experienced bleeding into any of these joints.

Both children are athletic. The haemophilic boy plays football for 1 h five times a week, cycles for 1 h three times a week, and goes swimming for 1 h once a week. His healthy counterpart cycles and plays football for 1 h once or twice a week. Both weigh 39 kg. The haemophilic child is 150 cm tall and the healthy child is 157 cm tall. The parents encourage these sporting activities. The main differences were seen in the comparison of femoral and tibial angle at zero and analysis from the side and from behind, in acceleration during knee bends from the side and from behind, and in the balance test viewed from above and behind.

**Femoral angle at zero**

Viewed from the side, the femur of the healthy 12-year-old (Fig. 27.4, top left) describes a rhythmic sinusoidal profile with balanced movements in the direction of extension and flexion, respectively. The tibial curve follows a sinusoidal profile like the femur, with no more than a slight flattening at the turning point. The curve described is symmetrical to the femur and in itself.

Lateral stabilization was difficult, as was the case with all the children measured, and a loss of rhythm was apparent which can be seen in the extension–flexion phases. The arrow (Fig. 27.4, top right) shows one of these deviations, which, however, point in the same direction.
The haemophiliac boy displays a different femoral curvature pattern. Figure 27.4 (bottom left) shows a loss of the sinus curve at the turning point, especially in the inversion phases, with a wavy curve form and several changes of direction in this phase. The sinus is flat and plateau-like, the angular deflections are not uniformly the same height and decrease with frequent repetition.

The tibia displays less abnormalities. The sinus is almost preserved and the deflections do not decrease in size, remaining rhythmic and constant. In the view from behind (Fig. 27.4, bottom right), the major discrepancy is in lateral stabilization with some instances of deviation of the femur and tibia in different directions.

Summary assessment

The haemophiliac child displays loss of sinusoidal curvature and rhythm in an analysis of internal knee kinematics, suggesting defective motion in the knee joint.

Angular acceleration in the knee joint

The defective motions presented in Fig. 27.4 are more apparent in the analysis of angular acceleration (Fig. 27.5). Although the acceleration rates for extension and flexion are the same in both children at a maximum of ±300°/s², the healthy boy displays an almost normal repeatable angular acceleration pattern with a sinusoidal curve and no major changes in direction during the extension-flexion phase (Fig. 27.5, circle, top left). The maximum values in the view from behind are +20 and −30°/s² in the healthy child. This shows that the deviation is wide (Fig. 27.4, top right) but muscle control is good (Fig. 27.5, top right).

The haemophiliac child has the same maximum values as his healthy counterpart, but displays three changes of direction in a phase where the healthy child shows only one change of direction. This is indicative of a major disruption of co-ordination in internal knee kinematics (Fig. 27.5, bottom left). The effects of acceleration are even clearer in the view from behind. Although the deflection pathway is virtually identical, the incongruence
of this effect results in a high angular acceleration of $+600$ and $-400/\text{s}^2$. This correlates with a much higher load and more problems with lateral stabilization.

Comparison of the two boys' sense of balance will show whether these internal knee motion abnormalities are a manifestation of a knee-specific problem or a general co-ordination disorder (Fig. 27.6, balance of shoulder co-ordinates in acceleration viewed from above and behind). Let us look first of all at the pattern displayed by the healthy child. Figure 27.6 (top left) shows rotational acceleration. We can see that rotation to the right is dominant. The values are highly irregular and off-balance, ranging from $70\,\text{cm/s}^2$ to the right to $30\,\text{cm/s}^2$ to the left. The view from behind, i.e. the upward and downward movement of the shoulders, displays a more symmetrical distribution and a maximum acceleration of $\pm 150\,\text{cm/s}^2$.

The haemophiliac boy displays a very different pattern. He stays symmetrical and remains in equilibrium at elevated acceleration rates of $\pm 110\,\text{cm/s}^2$ both in rotation and viewed from behind in the right–left symmetry analysis at acceleration rates of up to $\pm 400\,\text{cm/s}^2$. In particular, the slight sinusoidal upswing of maximal acceleration values in the right–left balance analysis (Fig. 27.6, bottom right) indicates a better sense of balance.

**Conclusions**

This study cannot provide statistically significant results but does indicate trends. In age-matched populations we saw more internal joint motion abnormalities in haemophiliac children than in healthy children. Variation in sinusoidal (physiological) motion was greater in the younger children in both study populations. Symmetry and balance improve as the children grow older.

The outcomes are best illustrated on the basis of the two 12-year-old boys. Although the haemophiliac child had no clinical, radiological or subjective symptoms, he displayed abnormalities of knee kinematics compared with his healthy counterpart that were not apparent by any other diagnostic procedure. We showed that the differences during stress (knee bends) were greater than while the children were walking on the treadmill. In some children we tested, the haemophiliacs with abnormal joint kinematics displayed better co-ordination than their healthy counterparts.

Considering such cases, we think it is fairly unlikely that a disease-related impairment of overall co-ordination is responsible for the outcome in an individual joint. We think the kinematic changes in the knee joints might be the functional correlate of a subclinical bleeding episode where the tiniest traces of blood may have provoked local inflammatory reactions at a subclinical level which the individual would not have noticed. We know from previous studies that minor changes in joints may affect functional performance. Left untreated, these functional impairments may progress, leading to morphological changes in the joint.

This study is a first step but a larger study involving more children is required in order to obtain conclusive results. This back-up study is to be performed in six haemophilia treatment centres in Germany over the next 2 years. The initial results will be enhanced by a follow-up measurement 1 year later. The data obtained may provide us with a basis for issuing recommendations to help prevent such functional knee joint abnormalities in young haemophiliacs at a very early stage.

**References**

CHAPTER 28

The haemophilic shoulder

C.J. Petersson

Introduction

The shoulder has never been considered to be a major haemophilic orthopaedic problem and only a few studies covering this subject have been published. In a study on haemophilic arthropathy of the upper limb, Högberg et al. [1] found that the glenohumeral joint was affected only in a small proportion of patients. In contrast, MacDonald et al. [2], analysing haemophilic arthropathy of the shoulder in 41 adult haemophiliacs, found shoulder symptoms in 15 patients. After radiology and ultrasound examination they concluded that rotator cuff tears are a common component of haemophilic arthropathy of the shoulder. In a recent review article, Gilbert et al. [3] concluded that the shoulder is a neglected joint in patients with haemophilia. They had found in an earlier study on upper extremity problems that, over a 5-year period, only 3% of all bleeding episodes occurred at the shoulder, comparable to the results of Duthie [4] evaluating 366 haemarthrosis in 113 patients during a 3-year period. He found shoulder haemarthrosis in eight patients (2%).

Malmö Haemophilia Centre experience

At the Malmö Haemophilia Centre the prevalence of shoulder symptoms in haemophiliacs has been evaluated twice, separated by a time interval of about 30 years. In the first study, performed in the early 1960s, the patients were representative of haemophilic patients before the era of modern treatment. A total of 157 patients, 114 with haemophilia A and 43 with haemophilia B were examined. There were 95 severe, 38 moderate and 24 mild haemophiliacs [5]. Twenty-one patients (13%) had symptomatic shoulder arthropathy and seven had bilateral symptoms. Nine out of 28 shoulders with arthropathy (one-third) were found in patients below the age of 30 years. The youngest patient with shoulder arthropathy was a 7-year-old boy with restriction of motion, muscular atrophy of the head of the humerus radiologically.

The second investigation of haemophilic arthropathy at our centre was made in the early 1990s. Ninety-six patients with severe or moderate haemophilia, 77 with haemophilia A and 19 with haemophilia B were then examined and their joints were evaluated and scored according to the World Federation of Haemophilia (WFH) system. Table 28.1 shows the age and arthropathy distribution in the patient group demonstrating a very low prevalence of arthropathy in small boys and teenagers with modern prophylactic haemophilia treatment. Shoulder haemorrhages or arthropathy symptoms were not found in any patient below the age of 35 years. Fifteen patients had shoulder arthropathy symptoms. Nine had bilateral arthropathy and all patients with shoulder arthropathy had concomitant arthropathy in several other joints (Table 28.2). This seems to indicate that isolated shoulder haemorrhages and shoulder arthropathy in haemophiliacs with prophylactic treatment are uncommon.

Table 28.1 Patient and arthropathy data of 96 haemophilia patients.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total number of patients</th>
<th>Haemophilia type</th>
<th>Number of patients with arthropathy</th>
<th>Number of patients with shoulder arthropathy</th>
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<tbody>
<tr>
<td>0–10</td>
<td>18</td>
<td>16/2</td>
<td>14/4</td>
<td>1</td>
</tr>
<tr>
<td>11–20</td>
<td>22</td>
<td>18/4</td>
<td>18/4</td>
<td>12</td>
</tr>
<tr>
<td>21–30</td>
<td>18</td>
<td>15/3</td>
<td>17/1</td>
<td>16</td>
</tr>
<tr>
<td>31–40</td>
<td>18</td>
<td>14/4</td>
<td>14/4</td>
<td>18</td>
</tr>
<tr>
<td>41–50</td>
<td>14</td>
<td>12/2</td>
<td>8/6</td>
<td>14</td>
</tr>
<tr>
<td>51–60</td>
<td>2</td>
<td>1/1</td>
<td>1/1</td>
<td>2</td>
</tr>
<tr>
<td>61 +</td>
<td>4</td>
<td>2/2</td>
<td>1/3</td>
<td>4</td>
</tr>
</tbody>
</table>

Sev/Mo, (severe/moderate)
Table 28.2 Clinical data of 15 haemophilia patients with shoulder arthropathy.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Type of haemophilia</th>
<th>Shoulder</th>
<th>Clinical evaluation score</th>
<th>Concomitant arthropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>A s</td>
<td>Right</td>
<td>5</td>
<td>e, h, k, a</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>B s</td>
<td>Left</td>
<td>4</td>
<td>e, k, a</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>A s</td>
<td>Right + Left</td>
<td>2 + 2</td>
<td>e, k, a</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>A s</td>
<td>Right</td>
<td>1</td>
<td>e, k, a</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>A s</td>
<td>Left</td>
<td>3</td>
<td>e, k, a</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>A s</td>
<td>Right + Left</td>
<td>3 + 2</td>
<td>e, h, k, a</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>A s</td>
<td>Right + Left</td>
<td>4 + 3</td>
<td>e, k, a</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>A s</td>
<td>Right</td>
<td>7</td>
<td>e, k, a</td>
</tr>
<tr>
<td>9</td>
<td>44</td>
<td>A mo</td>
<td>Right + Left??</td>
<td>3 + 2</td>
<td>e, k, a</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>B s</td>
<td>Right + Left</td>
<td>4 + 4</td>
<td>e, h, a</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>A mo</td>
<td>Right + Left</td>
<td>3 + 5</td>
<td>e, k, a</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>A mo</td>
<td>Left</td>
<td>3</td>
<td>e, k, a</td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>B s</td>
<td>Right + Left</td>
<td>4 + 4</td>
<td>e, h, k, a</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>A mo</td>
<td>Right + Left</td>
<td>2 + 4</td>
<td>e, h, k, a</td>
</tr>
<tr>
<td>15</td>
<td>69</td>
<td>B mo</td>
<td>Right + Left</td>
<td>2 + 2</td>
<td>e, h, k, a</td>
</tr>
</tbody>
</table>

a, ankle; e, elbow; h, hip; k, knee; mo, moderate; s, severe.

One patient with moderate haemophilia B, aged 69 years, had cuff tear symptoms bilaterally. The other patients had shoulder arthropathy symptoms with restriction of motion and periods of mild to moderate shoulder pain. No patient in our study group had continuous severe shoulder pain. Unfortunately, it was not possible, at the time of our study, to perform magnetic resonance imaging (MRI) studies of the shoulders but radiological shoulder examinations were performed.

The results of the radiological examinations indicate that the changes already described by several authors [3–5] in haemophilic shoulders are pathognomonic: cystic changes in the head of the humerus, narrowing of the joint space and distally pointing osteophytes of the head of the humerus and the glenoid (Figs 28.1 and 28.2). Epiphysial enlargement, characteristic of haemophilic arthropathy of other joints, was not seen in the shoulder of the present study but the large observed osteophytes might be caused by hyperaemic and/or cytokinetic stimulation. In rheumatoid arthritis of the shoulder, destructive synovitis eroding the surface margins of both the humeroscapular and acromioclavicular joints and giving typical radiological findings, is seen in increasing frequency with disease duration [6, 7]. No haemophilic patient in our study group had these radiological findings and none had proliferated bursitis sometimes seen in rheumatoid patients. Therefore, it is likely that the pathophysiology behind the destructive arthropathy in haemophiliacs giving rise to the characteristic radiological findings is following another pathway.

**Treatment**

Patients with acute shoulder bleedings should be treated with replacement of the missing factor, followed by arm rest until the pain subsides. In patients with very severe shoulder pain it is
Fusion or prosthetic shoulder replacement are alternative surgical procedures that can be offered patients with painful disabling advanced arthropathy. Luck and Kasper [10] described five patients who were treated with shoulder fusion using a single screw or, in two cases, three-plane shoulder fusion with good functional results even if the fusion was fibrous in two cases. Luck and Kasper [10] also reported three prosthetic shoulder replacements using the Neer II prosthesis with cement. Two patients were pain-free and one had occasional minimal pain postoperatively. Shoulder flexion and abduction improved slightly compared with preoperatively and shoulder rotation was reported better than that after shoulder fusion. Radiolucency at the cement–bone interface did not progress during a 6-year follow-up period. At the Malmö Haemophilia Centre shoulder replacements have been offered to three patients with limited shoulder motion and radiologically advanced arthropathy but hitherto no patient has considered his shoulder arthropathy so painful or disabling that he has wanted this procedure.

Conclusions

The complex relationship between recurrent joint bleeding, synovitis and the development of crippling arthropathy has been extensively studied and elucidated in human biopsy and necropsy studies as well as experimental investigations. However, the cause of joint destruction in haemophilia is not yet clear. Many studies have found iron deposition in synovium and cartilage, in enzymes released into joints and inflammatory responses to cells and lymphokines as aetiological factors. However, the mechanism remains to be precisely defined. One question still lacking an answer is why the knee, elbow and ankle are the joints most often affected by haemophilic haemorrhages, synovitis and destruction. Bleeding and arthropathy of the shoulder are, according to our and others’ experience, less frequent and modern prophylactic factor treatment seems to be able to reduce the incidence of shoulder arthropathy further [11]. In future, very few small boys and adolescents on a prophylactic haemophilia treatment programme will present with shoulder symptoms. Adult haemophiliacs with symptomatic shoulder synovitis or arthropathy can be offered various treatment options. However, according to the experiences at the Malmö Haemophilia Centre, the need for surgical procedures will remain low.

References

Osteonecrosis of the femoral head in haemophilia

I. Hvid

Introduction

Avascular necrosis of the femoral head (AVN) is now rare in haemophilia, probably even rarer than in a non-haemophilia population. However, before specific prophylactic treatment became available, the incidence was quite significant [1,2]. Primary or idiopathic AVN occurs in both children and adults; in children it is known as Perthes disease. In secondary AVN there is an external cause with a more or less apparent influence on femoral head circulation.

Femoral head circulation

The reason why osteonecrosis is seen more frequently in the femoral head than in other locations has to do with the special arrangement of the blood supply to the femoral head [3]. The medial and lateral circumflex arteries run anterior and posterior to the base of the femoral neck forming an extracapsular vascular loop. A limited number of branches from this loop perforate the joint capsule at the base of the neck. From here, they run a distance on the surface of the bone of the femoral neck, leaving them vulnerable to increased intra-articular pressure, then perforate the bone to become intrasosseous.

In the very young child, some of these intrasosseous arteries will traverse the growth plate and contribute to the perfusion of the femoral epiphysis. However, after approximately age 3 years, these transphyseal vessels are no longer found, and the epiphysis is entirely dependent for nourishment on inferoanterior and superoposterior groups of vessels running intra-articularly on the femoral neck all the way from the base of the neck to the epiphysis, traversing superficial to the growth plate. Contrary to previous belief, the vessels of the teres ligament of the femoral head contribute no significant perfusion to the femoral head in the child until approximately aged 8 years, then increase slightly in importance with time to contribute a maximum of 20% in the adult. After closure of the growth plate around age 14 years in the female and age 16 years in the male, again there may be vessels joining the metaphyseal and epiphyseal vascular beds.

Because of this particular vascular arrangement, the circulation of the femoral head is vulnerable. Dislocated femoral neck fractures or acute epiphysiolysis may easily cause rupture of the vessels, and even if some vessels are maintained, increased articular pressure from bleeding and effusion may compress intact vessels. In children, effusion alone may cause sufficient compression of the vessels of the femoral neck to produce femoral epiphyseal hypoxia and partial or total cell death in this small but crucial bone compartment. Pressure from outside the hip joint is thought to be important in AVN secondary to treatment of developmental dysplasia of the hip (congenital dislocation), and after reduction of the hip it is important to not immobilize the hips in too much abduction to minimize this complication.

Avascular necrosis in haemophilic children

Perthes disease (Fig. 29.1) is seen in children between 3 and 11 years of age with peak incidence around age 7. The prevalence in Scandinavia is about 1 in 10 000 children younger than 15 years [4]. In a study comparing haemophiliac patient populations before and during the era of prophylaxis, a prevalence of 4/63 (6%) in patients not on prophylactic treatment was found, while in 44 patients receiving prophylactic treatment no evidence of Perthes-like changes of the femoral head was found [1]. This would indicate that in haemophilia, the aetiology of Perthes-like changes is mainly haemarthrosis. This opinion was already voiced by Winston in 1952 [5], who described seven cases of haemophilic arthropathy of the hip, five of which were in children of which four had radiographical signs of AVN. The youngest child with AVN was 18 months old at diagnosis, and had very severe changes of the hip 12 years later. In a radiological survey of the hips of 107 patients with haemophilia, three cases of AVN were identified in patients between 6 and 12 years of age [2]. It is not clear whether adult patients were included in the study because the age range of the patient cohort is not given. These cases were described as ‘silent’, and significant haemarthrosis was not thought to have preceded development of AVN.

In non-haemophilic children, the cause of the disease is unknown. Synovitis is present and the severity correlates with the extent of osteonecrosis as seen on radiographs or magnetic resonance imaging (MRI) [6]. Although the synovitis could
have aetiological significance, it might well be a secondary occurrence. Intuitively, one would think of hypercoagulation or hypofibrinolysis as candidates in the search for a central aetiological factor in Perthes disease, and in 1996 a study was published showing abnormalities of coagulation or fibrinolysis in 75% of Perthes patients [7]. Unfortunately, other researchers were unable to reproduce these results [8,9], and thrombophilia as an aetiological factor in Perthes disease appears to be present only in a small fraction of patients. Other constitutional and environmental factors may be important, among them passive smoking [10] which may indirectly influence coagulation or fibrinolysis. To the extent that Perthes disease is secondary to inherited or acquired thrombotic disorders, haemophilia would be likely to protect against this aetiological pathway, and because haemarthrosis, as indicated above, is a very likely candidate in causing osteonecrosis of the immature femoral head in haemophiliac patients, this should be thought of as secondary AVN rather than Perthes disease.

In relation to pathogenesis and treatment, however, the above discussion is semantic. The disease runs through the same stages of condensation, fragmentation and repair as does Perthes disease [1,11], and the general principles of treatment in the absence of acute haemarthrosis would be the same. In the few cases reported in the literature, it appears that the radiographical results of treatment, which are likely to correlate with the long-term results and the risk of secondary osteoarthrosis, are less favourable [1,11]. The natural history of Perthes disease is dependent upon the age at onset, relatively high age being a poor prognostic indicator; the extent of osteonecrosis [12]; and the pattern of osteonecrosis [13]. Until recently, there was no really convincing evidence that any treatment would improve the natural history of the disease [14], but it appears that a North American multicentre prospective study is now providing evidence that active treatment based on the principle of containment is helpful in younger patients (6 years of age or younger) with severe disease (Herring lateral pillar group C)
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and older patients (7 years of age or older) with medium severity of the disease (Herring B), while the prognosis in older patients with severe disease (Herring C) remains poor.

Acute haemarthrosis of the hip in children on prophylactic treatment is rare. When it does occur, intensified factor treatment is indicated, bed rest with the leg supported in 45° of flexion [1], some abduction and external rotation to minimize pressure in the joint, and aspiration of the joint should also be considered to reduce the intra-articular pressure after factor substitution has commenced. Repeated ultrasound examination (Fig. 29.2) is helpful in diagnosing haemarthrosis and monitoring the effect of treatment. MRI can detect osteonecrosis before it becomes apparent on radiographs, but there is no real consequence of this finding other than perhaps modifying the physical activity of the child.

Fig. 29.2 Ultrasound examination of both hips showing: (a) effusion on one side; and (b) normal findings on the other.

Avascular necrosis in the adult

Osteonecrosis is a final common result in a number of conditions leading to bone death [15]. It is most commonly located to the femoral head. The main predisposing factors are trauma, glucocorticosteroids, alcoholism and connective tissue disorders. In about one-third of cases no predisposing factor can be identified, and these are therefore labelled idiopathic osteonecrosis. The incidence in the USA is estimated to be 15 000 new cases annually [15], equivalent to approximately 5 in 100 000. The incidence of AVN in haemophilia is not known, but clinical manifestations are rare. In Winston’s [5] series of seven patients, only two were adults, and only one of those showed collapse of the femoral head. The other case, a man of 30 years, might be the more interesting; radiographically, the femoral head was broadened and flattened (coxa magna) with cystic changes centrally, but with an otherwise well-preserved joint. This might have been the result of AVN of childhood, bearing some resemblance to a healed Perthes lesion. However, repeated haemarthrosis without AVN leads to epiphyseal overgrowth [16], which in the proximal femur might produce exactly the features of coxa magna. Reports on adult AVN in patients with haemophilia are extremely sporadic, and those often quoted turn out to report childhood AVN almost exclusively. The case reported by Rodriguez-Merchan et al. [17] was 18 years old, and did not have conclusive evidence of osteonecrosis on microscopical examination, and therefore this case might well have had the radiographical changes established during childhood. It is noteworthy that the case was identified from radiographical material ranging over 20 years in a larger centre. This would tend to indicate that adult-onset AVN is indeed very rare in haemophilia.

Disorders of coagulation have been implicated to be of etiological importance in idiopathic AVN [18,19]. Glueck et al. [19] examined 31 patients with non-traumatic AVN: 18 idiopathic and 13 secondary to glucocorticoid treatment or alcoholism. In the idiopathic group, 83% had coagulation disorders, while in the secondary group 62% had such disorders. Interestingly, increased levels of von Willebrand factor has been reported in both idiopathic and secondary AVN [20]. It is conceivable that haemophilia would effectively eliminate hypercoagulation and hypofibrinolysis as causes of AVN, lending strong support to the notion that AVN must be rare in haemophilia, unless significant haemarthrosis of the hip were prevalent—which is not the case.

When AVN does occur, it should probably be treated surgically like any other case of AVN. Hip pain in an adult haemophiliac should primarily lead to radiographical examination. If frank haemophilic arthropathy is not apparent, MRI should follow to explore the possibility of AVN because MRI is sensitive and specific in this condition [21]. Several staging systems have been proposed for AVN (see for example [22]). Early cases may benefit from core decompression [23] or vascularized structural bone grafting [24]. In more severely affected cases, total hip arthroplasty is indicated. In older patients (> 50 years)
good results can be expected. In younger patients, however, the results are even less favourable than in younger patients with osteoarthrosis, with a revision rate in patients younger than 50 years of 50% having been reported [25]. This would lend support to attempting less radical surgical treatment whenever possible. Osteotomy is another treatment modality that should be considered in younger patients even in more advanced stages of necrosis. These patients do not fare well with core decompression, but in >75% of osteotomized patients the need for further surgery is postponed by at least 6 years [26]. In the future, growth and differential factors and tissue engineering principles may increase the possibilities to treat these patients with femoral head sparing surgical methods [27].

Conclusions

In children not under specific factor prophylaxis, the incidence of AVN is higher than the incidence of Perthes disease (idiopathic AVN of childhood). In both children and adults under prophylactic cover, haemophilia appears to protect quite effectively against AVN. This is in accordance with studies showing that at least some cases of Perthes disease, and most cases of adult idiopathic AVN, are secondary to hypercoagulation or hypofibrinolysis. Treatment of AVN in haemophilia follows the same basic principles as in non-haemophilic AVN. Acute haemarthrosis of the hip joint constitutes a significant risk of femoral head ischaemia as a result of the vascular anatomy, and should be treated aggressively by full factor replacement therapy, correct positioning of the limb to minimize intra-articular pressure, monitoring of haemarthrosis by repeated ultrasound examination and joint aspiration, if necessary, to reduce intra-articular pressure.

References

**Introduction**

The ankle joint is the third most commonly affected site for spontaneous intra-articular bleeding in severely affected patients following joint trauma, accounting for 14.5% of recorded bleeds; the knee accounts for 44% and the elbow for 25% [1]. The pattern of bleeding varies according to age. The ankle is most commonly affected during the second decade and the knee is the most frequent site of bleeding in the third decade. Once the joint has been subject to repeated bleeds, it becomes more vulnerable and ultimately becomes a ‘target joint’ with relentless deterioration in the function and comfort of the hind foot.

**Pathology**

The ankle behaves like other synovial joints subjected to frequent haemarthroses. Repeated bleeds lead to synovial hypertrophy and angioneogenesis so increasing the likelihood of further, often spontaneous, synovial and subsynovial bleeds. The resulting haemosiderin deposition and subsequent synovial cell death causes enzyme release leading to progressive destruction of the articular cartilage (Fig. 30.1).

**Clinical features**

In the early stages, bleeding episodes cause transient synovial swelling, pain and restriction of movement. As the condition
evolves, the synovial swelling becomes persistent and chronic, and full recovery of movement between bleeding episodes becomes less likely. If the ankle has been affected during childhood, there is an increased likelihood of the development of growth disturbances with a tendency to medial distal tibial overgrowth and a resulting valgus hind foot [2].

The more usual pattern is of progressive destruction of articular cartilage, which produces an increasingly painful stiff talocrural joint. The subtalar joint is affected later in the disease process. Radiographically, there is evidence of loss of joint space accompanied by anterior and posterior distal tibial osteophytes. Later there is progressive flattening of the dome of the talus, possibly resulting from avascular necrosis (Fig. 30.2).

There is a gradual loss of movement, particularly dorsiflexion and a tendency to develop an externally rotated foot during the stance phase. As the subtalar joint becomes involved, the hind foot becomes increasing stiff and the foot adopts a planovalgus position. This loss of movement is generally associated with secondary soft-tissue contractures, particularly of the Achilles tendon. The end-stage arthropathy produces a virtually ankylosed ankle (talocrural and subtalar joints) (Fig. 30.3). At this stage the lack of movement in the joint is generally associated with a reduction in both pain and bleeding tendency.

**Assessment**

**Radiological**

Plain anteroposterior and lateral radiographs of the ankle are generally sufficient to demonstrate the extent of joint involvement, but in cases of suspected impingement further lateral radiographs in dorsiflexion and plantar flexion may assist in confirming the diagnosis. The subtalar joint is best shown on computed tomography (CT) scan and magnetic resonance imaging (MRI) can demonstrate soft-tissue involvement and preradiographical changes of avascular necrosis of the talus.

The degree of joint involvement is generally measured using the Pettersson et al. classification [3]. However, there are certain radiographical findings that are specific to the ankle joint.

- Anterior and posterior marginal osteophytes.
- Valgus tilt caused by medial tibial overgrowth in childhood.
- Avascular necrosis of the talus leading to dome flattening and collapse.

It is important to assess the degree and extent of associated joint involvement, which can vary from 9% to as high as 37% of subtalar joints [4]. The incidence increases with rising age and predominantly affects the posterior margin of the posterior facet. As with other scoring systems, there is a variable correlation between the clinical and radiological features.
Clinical

Clinical rating systems for the ankle have been devised with the specific aim of assessing outcome following injury or surgery, and are not universally applicable to patients with haemophilia who generally have many joints involved. Ribbans et al. [5] went a long way towards devising a more global assessment score for ankle arthropathy with a high correlation between clinical and radiological features. Despite its limitations, this system is still probably the most reliable predictor of outcome in such cases.

Treatment

Non-operative

Conservative measures remain the mainstay in treating ankle arthropathy. Routine prophylaxis can largely eliminate severe arthropathy and is now used routinely in many units worldwide, and this should be our goal. On-demand treatment is more prevalent and is more likely to be associated with bleeding episodes. The management of such an episode follows standard guidelines and consists of adequate factor replacement, joint immobilization followed by rehabilitation and physiotherapy. Care must be taken to minimize the onset of a fixed contracture, especially equinus.

At the Royal Free Hospital, London, we have a long tradition of combined clinics and the physiotherapists have been especially involved in the treatment of early ankle problems. We have found that simple shock-absorbing heel pads are helpful in reducing pain and more recently we have been using custom-built rigid orthotics in an attempt to correct any incipient hind foot deformity. Early analysis of the results has shown a reduction in the degree of pain, an improvement in the weight-bearing patterns as shown on force plate gait analysis and an impression that the rate of decline and joint degeneration can be slowed. At the Royal Free, only 14% of our severe haemophilic teenagers used orthoses or boots compared to 47% in the over-30-year age group. When compared to ankle function on a modified Mazur et al. [6] score, for those scoring > 85 points (maximum 100) for both ankles only 6% used orthoses or boots, compared to 74% with a Mazur score of < 85 points.

The pattern is similar for the use of walking aids. Of our severely haemophilic teenagers, 14% used walking aids, compared to 24% in the over-30-year age group. When compared to ankle function on a modified Mazur score, those scoring > 85 points (maximum 100) for both ankles only 3% used walking aids, compared to 35% with a Mazur score of < 85 points [5].

There may be a role for intermittent intra-articular steroid injections for short-term localized pain relief but this has to be performed under factor replacement cover and, ideally, using X-ray localization. Synovectomy has a limited role in the management of chronic ankle arthropathy (see below) but there may be a place for synoviorthesis [7].

Surgical

Surgical intervention is only considered when conservative measures have failed. In patients with synovitis and recurrent haemarthroses but preservation of joint (cartilage) space, synovectomy may decrease pain and prevent recurrent bleeding. Release of contractures may lead to substantial functional improvement in patients with joint contractures resulting from bleeding into muscle or from compartment syndromes.

Synovectomy of the ankle can be undertaken by either open or arthroscopic means. Synovectomy is generally indicated in those patients with recurrent bleeds with little or no radiographical evidence of arthritis, and when synoviorthesis is felt to be inappropriate. The arthroscopic route is preferable but it is not a straightforward procedure in patients with haemophilia. An open synovectomy may be easier under the circumstances but risks further loss of ankle motion. Ankle arthroscopy is useful in assessing the true degree of articular involvement prior to definitive procedures such as synovectomy, joint débridement and excision of the prominent anterior osteophytes so as to restore motion (Fig. 30.4).

O'Donoghue [8] described excision of the anterior osteophytes for those patients with anterior ankle pain aggravated by dorsiflexion, in an attempt to restore the range of motion and to improve the degree of comfort. Its use should be restricted to only those patients with a congruous talocrural joint and no flattening of the talar dome. In our experience, any benefit is short-lived and further surgery, generally in the form of ankle fusion, has become necessary within 5 years.

Juxta-articular cysts are fortunately rare and generally follow repeated bleeds in the ankle joint. As they expand they threaten the integrity and support of the articular cartilage, when open curettage and grafting may become necessary. Repeated posterior compartment bleeds cause muscle fibrosis and atrophy with

Fig. 30.4 Post-joint débridement and excision of the anterior osteophyte (haemophilic ankle).
a progressive equinus deformity of the ankle. This can then be further aggravated by a flexion deformity at the knee. Thus, lengthening of the Achilles tendon may be indicated either as an isolated procedure or in combination with other measures.

Achilles tendon lengthening can be undertaken using a series of subcutaneous tenotomies if there is no associated capsular contracture. However, in more complicated cases an open Z-lengthening and posterior ankle capsulotomy is necessary. Occasionally, slow correction of deformity by means of a hinged Ilizarov external fixator system may be necessary in the presence of extensive soft-tissue involvement.

Pearce et al. [2] reported their experience with supramalleolar tibial osteotomy in young patients with evidence of distal medial tibial overgrowth and resulting hind foot valgus. The operation is restricted to those patients with a mobile subtalar joint, an angular deformity and no associated degenerative disease on X-ray.

arthrodesis of the ankle remains the standard for surgical treatment of end-stage arthropathy, which is generally associated with severe pain, deformity or repeated intra-articular bleeds. Fortunately, arthrodesis is the primary surgical treatment for the small joints of the foot and ankle and success can be assured provided care is taken over the final position.

The ankle should be fused in either a neutral position or in slight plantar flexion, neutral to slight varus, and a small amount of external rotation. Ideally, the talus should be positioned posterior under the tibia to shorten the lever arm acting on the remainder of the foot and the neutral to slight external rotation (10° maximum) of the talus minimizes stress on the already compromised subtalar joint. Luckily, this is the position that the haemophilic ankle tends to adopt and little intra-operative correction is required. This greatly facilitates the operation, which effectively becomes an in situ fusion.

While many techniques have been described, we currently favour a single medial incision and medial malleolar osteotomy to gain access to the joint. The articular surfaces can then be decorticated and two 1.5-cm diameter dowels are then cut, withdrawn, turned through 90° and replaced so presenting a continuous cancellous bone surface thus facilitating union. Further autogenous bone graft, taken from the inner aspect of the medial malleolus, is then packed into the joint and the position held with two staples. A plaster is applied and full weight-bearing is encouraged as soon as pain permits. In a small series of seven patients over a 5-year period all cases have united and pain relief has been achieved. As yet there is no place for ankle replacement in a haemophilic patient.

Conclusions

Until all our patients are treated with regular prophylactic factor replacement we will be still be faced with having to deal with ankle arthropathy. In the early phases, treatment is directed at managing acute bleeds, restoring function and preventing deformity. The progression may be slowed by the judicious use of orthotics, splints and boots. Recurrent bleeding episodes may be reduced by synovectomy, either chemical, radioactive or surgical. Deformity is best treated by soft-tissue release or re-alignment osteotomy and movement can be restored by joint debridement and excision of prominent osteophytes. Finally, painful end-stage arthropathy requires fusion (Fig. 30.5). There is as yet no place for ankle replacement.

Fig. 30.5 (a) AP, and (b) lateral views of an ankle fusion.
References


**Neurological lesions following musculoskeletal bleeding in haemophilia**

*J. York*

**Introduction**

Prior to the advent of effective and reliable clotting factor replacement for patients with haemophilia A and B, intracranial bleeding was the most common and most feared cause of death in this condition [1,2] with an estimated mortality of 70% [3,4] with frequent, often severe, neurological deficits in the survivors. This complication is still encountered in neonates with unrecognized haemophilia [5] and a 12% prevalence of intracranial haemorrhage in a large series of haemophilic children was recently reported [6] with an annual incidence of 2%. Other central nervous system complications include epidural or subdural spinal haemorrhage, which is fortunately rare, with less than 30 recorded cases in the literature since Tellegen first described the condition in 1850 [7].

Intra-articular and muscular bleeding, in that order, are the most frequent manifestations of haemophilia, usually following some degree of trauma but occasionally apparently occurring spontaneously. The proximity of major peripheral nerves in several specified sites adjacent to joints and muscles exposes them to damage from bleeding into these tissues. Where muscles are situated in confined osteofascial boundaries a haematoma may raise tissue pressure sufficiently to cause ischaemic muscle contracture following pathological changes, as documented by Duthie et al. in 1972 [8]. Muscle fibres die as the result of bleeding within the substance of the muscle, leading to infiltration by polymorphonuclear leucocytes and phagocytic mononuclear cells and increasing numbers of immature connective tissue cells. Clot resorption and the removal of necrotic muscle tissue is followed by fibrosis with no effective regeneration of muscle fibres following large haematomas [8].

In other circumstances, a haemophilic pseudotumour or muscle cyst may form [9]. Gilbert advocates that the term ‘pseudotumour’ should be replaced by ‘haemophilic blood cyst’ as the pathology of the lesion is better described in this way and its diverse effects on adjacent tissues more easily interpreted (personal communication, 2002). The potential sites of compressive nerve damage for intra-articular or intramuscular haemorrhage are listed in Table 31.1. The severity of functional impairment caused by pressure neuropathy ranges from transient neuropraxia, through axonotmesis with potential for recovery, to complete loss of function resulting from neurotmesis often with permanent severe motor and sensory deficit.

**Upper limb**

**Ulnar nerve**

The ulnar nerve at the elbow passes behind the medial epicondyle in the groove formed between it and the olecranon process of the ulna where it is superficially situated and closely related to the capsule of the humero-ulnar joint. While acute
elbow haemarthroses may produce transient nerve damage it usually responds to conservative treatment as the extrinsic pressure is rapidly relieved by effective factor replacement, but Cordingley and Crawford found intraneural bleeding in the ulnar nerve in a 9-year-old boy following a bump to the elbow [10]. Bony elbow changes such as cubitus valgus deformity and synovial hypertrophy as a result of chronic haemophilic arthropathy are more often associated with ulnar nerve dysfunction, at times producing a tardy ulnar palsy. Nerve conduction studies using surface electrodes provide localization of the level of the lesion and definition of its severity [11]. Surgical anterior transposition of the nerve may be necessary.

The ulnar nerve may also be damaged with the median nerve in the forearm as a result of intramuscular bleeding in the flexor muscles resulting in an anterior compartment syndrome. If prompt and adequate factor replacement treatment is available the likelihood of nerve damage is slight and the major hazard of ischaemic muscle contracture avoidable. Careful monitoring of intracompartmental pressure is available in most major centres and is important if replacement treatment is delayed, and the lack of this facility or the presence of a clotting factor inhibitor create major management problems.

A wide fasciotomy may be necessary if conservative treatment is unsuccessful and should only be undertaken by experienced surgical staff supported by advanced clinical and laboratory haematological services and adequate supplies of appropriate clotting factor. Unfortunately, this ideal situation is rarely available in some developing countries with unfortunate long-term sequelae for the patients.

**Median nerve**

The median nerve may be involved less commonly following elbow joint haemarthroses. It is more commonly compromised distally by bleeding in the tightly constrained carpal tunnel as a result of wrist joint or tenosynovial haemorrhage [12]. Factor replacement, splinting and graduated physiotherapy are usually effective treatment but if the nerve recovery is delayed the nerve may need to be explored and in one case report intraneural haemorrhage was noted [13].

**Radial nerve**

The radial nerve is rarely involved in the posterior compartment of the forearm [11].

**Lower limb**

**Femoral nerve**

Femoral nerve lesions are the most common peripheral neurological complication of haemophilia resulting from musculoskeletal bleeding and iliopsoas haematoma is more often causally implicated than hip joint bleeding. In some elegant anatomical dissections with injection studies, the iliacus muscle has been shown to be the initial site of haemorrhage with secondary involvement of the psoas [14].

The patient complains of pain deeply situated in the groin with radiation to the back or thigh and the thigh is held semi-flexed and any attempt at extension is limited by pain and spasm. Gentle rotation of the hip is not painful, differentiating the problem from a hip joint bleed, and the onset can be insidious and swelling in the right iliac fossa and abdominal guarding may mimic an acute appendicitis. On neurological examination, sensory loss is apparent over the anterolateral aspect of the thigh above the knee, and there is weakness of the quadriceps muscle and diminution or complete absence of the knee jerk. Computerized tomography is an effective diagnostic investigation (Fig. 31.1) and ultrasound and plain pelvic X-rays will usually demonstrate the enlargement in the psoas muscle but magnetic resonance imaging provides better anatomical definition.

The femoral nerve is formed from the L2, 3 and 4 nerve roots deep within the psoas major from which it emerges between this muscle and the iliacus muscle just above the inguinal ligament which it passes under to enter the thigh after giving off its lateral cutaneous branch. This branch is the sensory supply to the affected area of the thigh over the L2 and 3 dermatomes, while the motor fibres continue in the main trunk to innervate the quadriceps muscle and the knee jerk reflex. An iliacus haematoma occurs within a tight fascial compartment and blood is forced distally compressing the femoral nerve and may also extend into the adjacent psoas sheath.

Goodfellow et al. [14] suggest that primary psoas haemorrhage usually tracks proximally and is not associated with femoral neuropathy. The point is academic in the presence of appropriate physical signs. Early treatment is vital, with clotting factor replacement to maintain levels above 30% for 3-5 days and bed rest in the position of comfort over this time with the provision of adequate pain relief while avoiding intramuscular injections. Physiotherapy is then commenced with gentle passive stretching with prophylactic factor cover,
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leading on to active mobilization. Nerve function should be monitored clinically and nerve conduction studies arranged if recovery is delayed. Hydrotherapy is an effective adjunctive treatment.

Popliteal nerve
The popliteal nerve may be stretched during treatment to overcome flexion deformities of the knee in patients with haemophilia and after corrective splinting, either as a primary procedure or postoperatively after corrective surgery. Nerve function must be carefully monitored. If it becomes impaired, the splinting should be removed and the knee flexed to a further 20° or 30°. If nerve function does not respond, early complete motor recovery is rarely achieved [15].

Lateral popliteal nerve
The lateral popliteal nerve is vulnerable to injury as it runs round the head of the fibula either because of pressure from haemarthroses in the knee joint or the superior tibiofibular joint or, more commonly, as a postoperative complication following knee joint surgery such as total knee arthroplasty. If significant valgus deformity needs to be corrected during this procedure the risk of damaging the nerve is increased, and overenthusiastic retraction of the lateral side of the wound may also produce pressure neuropathy. Intraneural haemorrhage in this situation is rarely encountered and in most cases recovery usually occurs over a period of days or weeks. Where joint bleeding has caused the lesion, factor replacement is the indicated treatment. In postoperative cases this will be part of the protocol with continuous infusion or bolus replacement therapy. If recovery is delayed, electric nerve stimulation has been advocated but is of unproven value.

Tibial nerve
The tibial nerve can be damaged by a calf muscle haematoma which, more commonly, results in ischaemic muscle atrophy leading to shortening of the Achilles tendon, equinus ankle deformity and clawing of the toes. Where treatment is delayed or inadequate, permanent nerve damage and muscle contraction is likely.

Deep fibular nerve
The deep fibular nerve may similarly be compressed during bleeding into the anterior tibial compartment and may result from fractures of the adjacent tibia or fibula. In both situations, early effective replacement therapy has greatly improved the outcome.

Sciatic nerve
Sciatic nerve damage may occur during injudicious intramuscular injection into the buttocks, which should be avoided unless there is no other alternative when prophylactic cover should be used.

Haemophilic blood cysts (pseudotumours), depending on their situation, may also cause compressive nerve damage, more commonly in the lower limb [9].

General principles of treatment
Prevention is the most effective treatment and appropriate clotting factor should be administered as early as possible after an injury is suspected to elevate factor levels to 30% or above to stop further bleeding. Ideally, prophylactic treatment with recombinant factor VIII or factor IX, or viral and other effective agent-free human material to maintain levels of > 1% should be baseline treatment for all boys with haemophilia from an early age, transforming them into patients with moderate haemophilia.

This ideal can only be achieved in a small proportion of the world’s haemophiliaacs. The effectiveness of prompt conservative treatment is reflected in the sharp reduction in published series and case reports of both central and peripheral neurological complications from this disease in the literature in the last two decades. General exercise and, when necessary, physiotherapy to maintain muscle strength should be encouraged and supervised by family members and sensible boundaries negotiated to minimize risk-taking and other hazardous behaviour.

The availability of a haemophilia centre is a great advantage and surgical opinions should be sought early, especially if effective treatment is delayed. Pressure monitoring and surgical decompression may be required in acute compartment bleeding. The haemophilia nurse is usually the first contact and the centre should, where practicable, be separate from the emergency room with separate staffing and access to other services such as haematology, medical imaging and neurology.

Management problems
Inhibitors
The presence of a significant titre of clotting factor inhibitor complicates management and stretches resources. Low levels of an inhibitor may be neutralized by large doses of factor VIII or factor IX, or heterologous factor products such as porcine material may be available. Control of bleeding may require expensive agents such as recombinant factor VIIa [16] which can seriously compromise hospital and/or government budgets. The acute nature of these problem makes it unlikely that the patient would have had the inhibitor level lowered recently by techniques such as the introduction of immune tolerance or immunosuppression.
Muscle contracture and nerve damage

The end result in inadequately treated upper limb compartment syndromes is forearm muscle contracture such as in Volkmann’s ischaemic contracture with wrist flexion and loss of finger extension with varying levels of ulnar and median nerve dysfunction (Fig. 31.2). Osteotomy and fusion of the wrist joint and flexor tendon lengthening usually allow some functioning in the now more anatomically positioned fingers (Fig. 31.3). Similarly, calf muscle haematomas may cause muscle fibrosis and produce equinus deformities in the ankle and foot with clawing of the toes and disturbed gait (Fig. 31.4).

Surgical correction may require joint fusion, osteotomy, transposition of other tendons and lengthening of the Achilles tendon to achieve a satisfactory result. Measures to protect insensitive skin and prevent further damage to denervated joints are also important where nerve damage has occurred, as is physiotherapy to strengthen unaffected muscle groups. Details about these techniques can be accessed in surgical textbooks and monographs. The experience gained from the management of leprosy patients has provided new concepts of care in the neurological rehabilitation of peripheral nerve lesions [17].

Conclusions

In the developed world, the management of haemophilia has been dramatically improved by the introduction of prompt, safe and reliable replacement therapy and access to specialist centres of care. The improved prognosis of patients with haemophilia has allowed them to anticipate a future life with little or no significant long-term consequences, including neurological lesions from musculoskeletal bleeding in most circumstances. While the introduction of gene therapy has proved elusive, there is little doubt that it will ultimately become a practical reality and improved avenues of factor replacement availability and delivery are meanwhile being researched.

It is the plight of the 70–80% of the world haemophiliac population in developing countries without access to adequate treatment who present the greatest challenge. The innovative programmes in some countries are encouraging [18] as are the educational workshops and teams visits from experienced centres to strategic areas under the auspices of the World Federation of Haemophilia and the World Health Organization. Such visits not only help local health professionals but also graphically inform the visitors about the difficulties under which their colleagues work. They also create personal contacts facilitating opportunities for fellowships for appropriate workers to visit international haemophilia training centres for further experience.

References

Introduction

Haemophilic arthropathy is a disabling disease that can produce chronic pain, functional limitation and impair the quality of life of the affected person and his family. The condition is the result of repetitive intra-articular bleedings, which leads to the progressive destruction of the joints. In severe haemophilic patients, 85% of the bleedings occur in the articulations and the most affected joints are the ankles, knees and elbows [1]. Treatment with antihaemophilic factor concentrates improves the patient’s quality of life and his life expectancy [2]. The cost of the treatment of haemophilic arthropathy is high and has enormous socio-economic consequences in terms of the direct (life-long physical therapy, expensive orthopaedic surgery, antihaemophilic concentrates) and indirect (unemployment, lost days from school and work) cost of treatment [3–5]. The use of a primary prophylaxis in haemophilic patients is the only way to prevent the haemophilic arthropathy. However, prophylaxis is only possible in a small proportion of children with haemophilia because of its tremendous cost [6].

Cartilage degeneration

The pathogenic mechanism of haemophilic arthropathy is not fully understood. Although it is known that the condition is the result of articular haemorrhages, the necessary number and volume of bleedings for this disease to appear is still unknown [7,8]. It is important to understand the pathogenic mechanism of haemophilic arthropathy in order to treat it rationally. The compromise of the synovium and the progressive damage to cartilage are the result of articular bleeding [1]. Haemophilic arthropathy is present when a patient shows radiological changes indicating cartilaginous involvement [9]. The presence of blood in the articulation makes the synovial tissue become catabolically active and inhibits the synthesis of the articular cartilage matrix [10–12]. Roosendaal has shown that, in contrast to generally accepted ideas, blood has a direct harmful effect on cartilage irrespective of synovial changes [12].

In 1987, Carter et al. [13] calculated the subchondral deformations and stresses in the hip during weight-bearing using finite element models. In the areas of high joint contact pressure, high hydrostatic compression was correlated with cartilage thickness. The seldom contacting surfaces had lower hydrostatic compression and significant subchondral bone tensile strains tangential to the joint surface. The generation of tensile strains may promote the degenerative process by direct mechanical mechanisms. The tensile strains are associated with a reduction in the compressive hydrostatic stresses that facilitate cartilage degeneration and osteophyte formation.

In 1989, van der Kraan et al. [14] showed that the intra-articular injection of papain or iodoacetate interferes with cartilage metabolism resulting in osteoarthritic changes. In 1997, Buckwalter and Lane [15] published that people with abnormal joint anatomy or malalignment, joint instability, disturbances of joint or muscle innervation or inadequate muscle strength probably have increased risk of osteoarthritis.

Chronic articular synovitis in children leads to a local hyperaemia resulting in regional osteoporosis and bone enlargement, which results in deformities typical of haemophilic arthropathy. The decrease in the range of joint movement, muscular atrophy, leg length discrepancy and malalignment produce abnormal joint forces. As a result, the articulation suffers from two simultaneous phenomena that lead to its rapid impairment: one is biological (the presence of blood in the joint) and the other is mechanical (abnormal joint forces), which leads to articular overload. Many of the mechanisms responsible for the progressive loss of the cartilage remain unknown, but the process can be divided into three stages:

1. disruption of the cartilage matrix;
2. chondrocytic response to tissue damage; and
3. decline of the chondrocytic synthetic response and the progressive loss of tissue [16,17].

Failure to restore the tissue damage leads to the third stage in development of arthropathy. Alteration of subchondral bone includes formation of cyst-like bone cavities and the appearance of regenerating cartilage. This response is usually most
apparent on the periphery of the joint, where bone and cartilage form osteophytes. The affected synovium and the damage to the articular cartilage in haemophilic patients produce related structural changes in the joint. In consequence, when arthropathy develops, narrowing of the joint space, osteophytes and subchondral cysts appear (Fig. 32.1).

**Osteophytes**

Presumably, osteophytes represent a response to the degeneration of articular cartilage and remodelling of the subchondral bone, including the release of anabolic cytokines that stimulate cells proliferation and the formation of bone and cartilage matrices [18,19]. In 1999, van den Berg [20] demonstrated that in osteoarthritis excessive formation of growth factor TGF beta may contribute to cartilage lesion and osteophyte formation. Osteophytes usually develop around the periphery of the joint (marginal osteophytes), but they can appear along the insertions of the joint capsule (capsular osteophytes) [21]. In general, marginal osteophytes have a cartilaginous surface that resembles normal articular cartilage and they appear to be an extension of the joint surface.

In 1990, Pottenger et al. [22] described that in primarily unicompartamental osteoarthritis, marginal osteophytes appear to stabilize osteoarthritic knees, but can cause fixed deformity. The intra-articular osteophytes that protrude from degenerating joint surfaces are called central osteophytes [23]. In general, osteophytes do not require any treatment except when they limit the articular function or when they cause painful movements. A clear example of limitation in the articular function can be frequently seen in ankle arthropathies where the osteophytes of the anterior edge of the tibia of the upper margin of the talus lead to a limited dorsal flexion. These are the typical capsular osteophytes (Figs 32.2 and 32.3). When this limitation is present, the resection of the osteophyte is recommended, and if it is related to Achilles tendon shortening release is performed. The osteophytes that cause painful mobility are generally located in areas in direct contact with muscles and tendons.

Treatment consists in the resection of the osteophyte. The
Subchondral cysts

The first signs of arthropathy on X-ray are a narrowing of the joint space and small abnormalities in the subchondral bone. The subchondral cysts appear later, and are abundant, irregularly distributed and bigger than others that appear in children or adolescents. In 1959, Swanton [25], in his investigation in dogs, showed that these cysts are connected with articulation and are similar to those found in degenerative arthritis. Pathological studies have shown that in the subchondral bone there are thin atrophied bone sheets under the subchondral bone [26,27]. Cysts can be totally exposed in articulation accompanied by the disintegration of the subchondral bone and the articular cartilage, leading to the destruction of the joint. Sometimes the cyst progression is metaphyseal and results in an osteolytic lesion that may lead to a pathological fracture.

It is not yet known why some cysts evolve in this manner. Our experience shows that the appearance of these cysts is more frequent in lower limbs. In the knee, these cysts are usually located in the proximal tibia and, in the ankle, in the distal tibia. In the upper limb, cysts are observed in the elbow, affecting the olecranon, and in the shoulder, affecting the humeral head. The treatment differs according to the size of the cyst. If the cysts are smaller than 3 cm, they must be cleaned and filled with fibrin seal. If the cysts are bigger than 3 cm, they must be filled with bone graft taken from a tissue bank or by means of coralline hydroxyapatite (Figs 32.4 and 32.5). Since 1996 we have used coralline hydroxyapatite with excellent results [28]; it is easy to store and to apply and is not biologically risky.

Intraosseous cysts

Subchondral and intraosseous cysts must be differentiated. The latter appear in the bone, mainly in metaphysis and are not related to arthropathy. The pathophysiology is different and intraosseous cysts are caused by intraosseous bleedings. Treatment consists in aspiration of the cavity and filling with fibrin seal or a bone substitute, according to the size of the lesion [29].

The progression of the subchondral cyst to a large metaphyseal lesion is unpredictable. They can show different degrees of cortical destruction, such as thinning, erosion or pathological fracture. In the case of a pathological fracture secondary to a large metaphyseal cyst, treatment should consist of immobilization (brace) and aspiration and filling of the affected area. Large cavities should be filled with lyophilized bone graft or bone substitute such as coralline hydroxyapatite. The filling procedure is performed by manually pressing the graft into the cavity (bone packing). We do not use internal fixation to stabilize the fracture because of the poor bone quality in the region.

Conclusions

Haemophilic arthropathy is the result of repetitive intra-articular
bleedings. The mechanism of production is biological and mechanical. Haemophilic arthropathy is only prevented by primary prophylaxis. Related structural alterations, such as osteophytes and subchondral cysts, must be treated in an appropriate way in order to improve function, avoid pain and preserve the bone stock of the affected joint. These treatments will benefit patients and improve their quality of life.

Fig. 32.4 (a) Anteroposterior radiograph of the knee joint that shows a subchondral cyst-like bone cavity (arrows). (b) Lateral view of knee joint with cyst-like bone cavity (arrows). (c) Computed axial tomography of the cyst in the proximal tibia (arrows).

References

Fig. 32.5 (a) Anteroposterior and (b) lateral views of the knee joint following bone grafting of the lesion shown in Fig. 32.4 (1-year follow-up).
THE HAEMOPHILIC JOINTS: NEW PERSPECTIVES


CHAPTER

Haemophilic arthropathies: comparison between clinical, radiographical and subjective findings

T. Wallny, L. Lahaye, H.H. Brackmann, A. Seuser and C.N. Kraft

Introduction

There seems to be a general consensus in the literature that clinical and radiographical findings correctly depict the severity of haemophilic arthropathy [1–3]. Although joint pain is known to be the symptom that encumbers the haemophiliac most [4], this valuable indicator of the patient’s quality of life [5] usually obtains little attention from the physician during routine clinical and radiographical follow-up. Only in recent years have studies focused more on these important aspects [5–11].

Our study aims to focus the physician’s understanding and awareness towards the importance of joint pain for the haemophiliac. A particular focus of our work lies in determining whether there is a statistically significant correlation between clinical and radiographical results in haemophilic arthropathy and the patient’s subjective joint pain status. We hereby pursue the suggestion put forward by Miners et al. [8] to scrutinize more closely the relationship between haemophilic arthropathy and the patient’s quality of life by assessing possible correlations between objective parameters and patient self-evaluation.

This investigation aims to answer the following questions. To what extent can the treating physician draw conclusions from clinical and radiographical assessment of the haemophilic joint status on the severity of joint pain? Is the degree of objective joint damage (clinical and radiographical) correctly mirrored in the patient’s decline in quality of life?

Materials and methods

We interviewed 112 haemophiliacs in January 2000 by means of a questionnaire [12] concerning their subjective joint pain (visual analogue scale, VAS), social status and quality of life related to the year 1999. All patients had been in regular haematological and orthopaedic care (4 times per year) at the Haemophilia Care Unit of the Institute for Experimental Haematology and Transfusion Medicine, University of Bonn, for a minimum of 10 years, and all had, at some stage, at least one clinically painful joint. Prior to distribution by post, the non-validated questionnaire was read and evaluated by three haemophiliacs to judge whether it was understandable and self-explanatory. The questionnaire was self-administered, yet all patients had the opportunity of contacting a specialist by telephone. Of 112 patients, 79 (70.5%) returned the questionnaire and gave written consent for their data to be used for research.

The age range of the 79 haemophiliacs involved was from 18 to 63 years, with an average of 42.0 years and a median of 43.5 years. Seventy-six of the 79 (96.2%) had haemophilia A (74 severe, two moderate); the rest were haemophilia B patients. Hepatitis C was chronic in 82.3%, and 49.4% had human immunodeficiency virus (HIV). At the time of questioning, 72/79 haemophiliacs (91.1%) substituted factor concentrate regularly, not only in bleeding episodes. This was generally at least 3000 IU factor VIII/factor IX per week.

Clinical score

All available clinical and radiographical data concerning the typically affected joints (ankle, knee, elbow, hip and shoulder joints) of these 79 patients from the year 1999 were collected. Any data in connection with an acute bleeding episode or trauma were not evaluated. The clinical assessment of patients was performed by experienced physicians who knew and had looked after this group for many years. Joint damage was quantified by a scoring system which used the ‘clinical examination’ and ‘pain’ parts of the World Federation of Haemophilia (WFH) [13] scoring system, incorporating criteria such as ‘swelling’, ‘muscular atrophy’, ‘frontal plane axial deviation’, ‘crepitation on movement’, ‘range of motion’, ‘flexion–contraction’, ‘joint instability’ (0–12 points) and ‘pain’ (0–3 points). The total sum of these criteria is defined as the clinical joint score (range 0–15 points), whereby a joint with 0 points is clinically healthy and one with 15 points is clinically massively impaired. We then went on to define a clinical patient score, which is the sum of the
patient’s ankle, knee and elbow joint scores and has a range of 0–90 points.

**Radiographical measurements**

In 60/79 patients (75.9%) we were able to evaluate complete X-rays of the ankle, knee and elbow joints from 1997 to 2000. In the remaining 19 haemophiliacs, either X-rays of all clinically damaged joints were not complete (14 cases) or radiographs could no longer be evaluated for our study because of the implantation of artificial joints (five cases). The severity of haemophilic arthropathy on the X-ray was determined by utilizing the Pettersson Score [14]. The Pettersson Score incorporates the following eight criteria:

1. Osteoporosis;
2. Enlargement of epiphysis;
3. Irregularity of subchondral surface;
4. Narrowing of joint space;
5. Subchondral cyst formation;
6. Erosion at joint margins;
7. Incongruence between joint surfaces; and
8. Deformity (angulation and/or displacement of articulating bones).

The sum of these eight criteria led to the radiographical joint score (range 0–13), whereby 0 points suggests no radiographically evident pathological finding and 13 points shows a massively damaged joint on X-ray. The radiographical patient score was defined as the sum of the radiographical joint scores of ankle, knee and elbow joints (range 0–78 points). Clinical and radiological score were assessed by a single doctor.

**Questionnaire**

Using a visual analogue scale (VAS) in the questionnaire (Fig. 33.1) [12] that ranges from 0 to 10 (0 being no pain and 10 the most severe pain the patient can imagine), patients were asked to evaluate the individual pain level of their ankle, knee, hip, elbow and shoulder joints. We called this point score (VAS) for each individual joint the subjective joint score. The sum of the subjective joint scores of the ankle, knee and elbow joints then gave us the subjective patient score (range 0–60 points).

A section of the questionnaire, offering answers from which the patient could choose, aimed to determine the main reasons for pain, at what time of the day patients usually suffered the most intense pain, what was usually done to alleviate pain and the efficacy of pain-alleviating measures. Furthermore, we were interested in the type of painkillers taken as well as how the haemophilic patient subjectively judged their usefulness. We questioned patients as to the influence of pain on daily activities and to what degree they felt psychologically impaired because of pain. A further aspect evaluated was whether the patient’s social status was subject to change because of pain status or skeletal deformities.

**Statistics**

The clinical review on the one hand and the radiographical evaluation on the other served as our objective parameters concerning assessment of the severity of haemophilic arthropathy. Data collected from the questionnaire delivered all subjective patient-derived factors in connection to pain status and quality of life. Statistical evaluation was performed on a PC using the Statistical Package of the Social Sciences (SPSS, Version 9.0). Possible correlations between the clinical score and subjective pain score as well as between radiographical score and subjective pain score were assessed by means of the Spearman’s coefficient. Using the Mann–Whitney U-test we tested for significance between the clinical and radiographical patient scores and different answers of the patients to our questions. The level of significance was set at $P \leq 0.05$.

**Results**

Clinical, radiographical and subjective findings showed the ankle joint to be the most affected joint in the haemophilic (clinical and radiographical joint score > 0; VAS > 0, respectively). The second most frequently damaged joint was the knee, followed by the elbow, hip and then the shoulder (Table 33.1).

The average point score of the subjective VAS as well as the clinical and the radiographical score is shown in Table 33.2. The ankle was the most painful joint for our patients and also showed the most marked radiographical changes. Clinical damage was found to be similar to that of the knee. The largest discrepancy between objective and subjective assessment was found for the shoulder joint. Hip and shoulder joints were least often involved in haemophilic arthropathy. They were also the joints with the least clinical and radiographical impairment and were subjectively associated with the least pain (average values in the clinical and radiographical joint score as well as in the VAS < 1).

On average, our group had 4.4 clinically and 4.0 radiographically damaged joints and 3.5 joints were claimed to be manifestly painful. This value relates to the ankle, knee and elbow joints (minimum 0; maximum 6). The clearest correlation between subjective and objective results was found for the knee, followed by the ankle; the elbow did not show any useful correlation in this respect. In Table 33.3 the Spearman’s coefficients are shown regarding the target joints; a coefficient $< 0.5$ was considered to be too low to demonstrate a strong correlation.

Figures 33.2 and 33.3 compare the joint scores of the clinical and radiographical data as well as the score for the subjective pain status (VAS) for the right knee joint. The linear regression demonstrates the correlation: the more clinical impairment (Fig. 33.2) and radiographical damage (Fig. 33.3) that was found, the more the patient claimed to suffer from pain. Interestingly, the intersection of the linear regression with the y-axis
Please consult the following visual analogue scale (VAS), concerning your pain threshold, and then answer the following questions:
(10 on the scale is the worst pain you can imagine, and 0 is no pain at all).

<table>
<thead>
<tr>
<th>Localization</th>
<th>Major pain region?</th>
<th>Where else do you suffer from pain?</th>
<th>What is the quality of your pain? (a, stabbing; b, persistent; c, burning; d, sudden-onset; e, dull; f, bright).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other joints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is the most frequent reason for your joint pain?
○ Bleeding episodes ○ Chronic joint pain ○ Pain after rest
○ Pain during movement ○ 'Wrong' movement ○ Climbing stairs ○ Other

Do you have pain throughout the day?

a) Without medication ○ Yes ○ No ○ Occasionally
b) After injection of factor ○ Yes ○ No ○ Occasionally
c) After factor and use of other medication ○ Yes ○ No ○ Occasionally

At what time of day are your pain symptoms worst?
○ Morning ○ Midday ○ Afternoon ○ Evening ○ Night

Did your pain symptoms alter your daily activities as well as your requirements over the past year?
○ No ○ Occasionally ○ Moderately ○ Significantly

Were you in low spirits over the past year because of your pain-symptoms?
○ No ○ Occasionally ○ Frequently ○ Constantly

Please estimate the pain level you find tolerable in daily life (circle the appropriate number):

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td></td>
<td>Worst-imaginable pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Were you able to alleviate your pain?
○ No ○ Slightly ○ Markedly ○ Completely

Are you in constant need of medical treatment because of joint pain (apart from bleeding episodes)?
○ Yes ○ No

Fig. 33.1 Pain questionnaire.
Which treatment was performed to alleviate pain in joint?  
(please use 1 for regular and 2 for occasional treatment)

<table>
<thead>
<tr>
<th>Localization</th>
<th>Factor-concentrate</th>
<th>Pain killers</th>
<th>Cortisone</th>
<th>Ointments</th>
<th>Stabilizing bandages</th>
<th>Orthopaedic shoes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder right</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Shoulder left</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow right</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Elbow left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip right</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hip left</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee right</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Knee left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other joints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you take painkillers, what drug do you use? Please name all medication below:

- Factor-concentrate
- Pain killers
- Cortisone
- Ointments
- Stabilizing bandages
- Orthopaedic shoes

in which doses
- 1 x daily
- 2 x daily
- 3 x daily
- More frequently
- Only when needed

Do the painkillers sufficiently alleviate your pain?
- Yes
- No

Do you perform exercises / physical therapy to train muscles and joints (i.e. cycling, swimming, gymnastics)?
- Daily
- 2–3 times per week
- Once per week
- Less than once per week

Were you ill from work more than twice in 1999 because of joint pain?
- Yes
- No

Have you prematurely been retired because of your joint pain?
- Yes
- No

Fig. 33.1 (cont'd)

lies above 0 in the positive area. This indicates that patients only suffer from pain with a certain degree of clinical or radiographical damage to the joint (Figs 33.2 and 33.3).

Of our patients, 36/79 (45.6%) claimed to have pain throughout the day if they did not take any painkillers. Despite the use of factor concentrates and analgesic drugs, 9/79 haemophiliacs (11.4%) suffered pain throughout the day. The most severe pain was either in the morning (38/132; 28.8%) or in the evening (47/132; 35.6%). In declining frequency, factor concentrates, non-steroidal anti-inflammatory drugs (NSAIDs) and modified orthopaedic shoes were used to curb pain (157/227; 69.2%).

Of the 48/79 patients using oral painkillers, 21/48 (43.8%) did so on a regular basis. The most popular analgesic drugs were the NSAIDs acemetacin and diclofenac. Almost one-third of all the haemophiliacs (15/48; 31.3%) claimed that the analgesic effect of oral painkillers was not sufficient, and 43/79 (54.4%) stated that they were frequently not able to curb pain at all. Concerning the patient score, the following became evident: the more damaged ankle, knee and elbow joints were found to be, the more difficult it was to achieve adequate pain-relief. The comparison of the medians of the patient score and the radiographical score in those patients with poor pain-relief (median 24.0 patient score and 43.0 radiographical score) and those with sufficient pain-relief (median 18.0 patient score and
Table 33.1 Number of affected joints.

<table>
<thead>
<tr>
<th>Joints</th>
<th>Subjective score</th>
<th>Clinical score</th>
<th>Radiographical score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Ankle</td>
<td>67% (53/79)</td>
<td>70% (55/79)</td>
<td>86% (68/79)</td>
</tr>
<tr>
<td>Knee</td>
<td>61% (48/79)</td>
<td>66% (52/79)</td>
<td>75% (59/79)</td>
</tr>
<tr>
<td>Elbow</td>
<td>44% (35/79)</td>
<td>41% (32/79)</td>
<td>62% (49/79)</td>
</tr>
<tr>
<td>Hip</td>
<td>9% (7/79)</td>
<td>8% (6/79)</td>
<td>14% (11/79)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>9% (7/79)</td>
<td>11% (9/79)</td>
<td>10% (8/79)</td>
</tr>
</tbody>
</table>

Table 33.2 Average points of visual analogue scale (VAS), clinical and radiographical score.

<table>
<thead>
<tr>
<th>Joints</th>
<th>Subjective score (VAS)</th>
<th>Clinical score</th>
<th>Radiographical score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Ankle</td>
<td>2.7</td>
<td>2.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Knee</td>
<td>2.4</td>
<td>2.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Elbow</td>
<td>1.5</td>
<td>1.3</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 33.3 Spearman correlation: VAS (subjective) vs. clinical and VAS vs. radiographical assessment.

<table>
<thead>
<tr>
<th>Joints</th>
<th>VAS vs. clinical score</th>
<th>VAS vs. radiographical score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.512</td>
<td>0.474</td>
</tr>
<tr>
<td>Knee</td>
<td>0.641</td>
<td>0.663</td>
</tr>
<tr>
<td>Elbow</td>
<td>0.460</td>
<td>0.411</td>
</tr>
</tbody>
</table>

Fig. 33.2 Visual analogue score (VAS) vs. clinical score (World Federation of Haemophilia).

Fig. 33.3 Visual analogue score (VAS) vs. radiographical score (Pettersson).

27.5 radiographical score) showed a marked divergence of these values. However, these discrepancies were not found to be significant in the Mann–Whitney U-test.

Half the patient group (40/79; 50.6%) acknowledged themselves to be significantly or even massively encumbered in activities of daily life because of constant or recurrent pain and disclosed that their quality of life was moderate because of frequently being in low spirits. A connection between the patient's moods and his joint status (sum of the joint scores of ankle, knee and elbow joints) was found. The higher the clinical and radiographical scores, the more the patient claimed to suffer
from depressive spells and acute changes of mood as well as decrease of daily activities: patients with relatively low objective scores (median clinical score 18.5 and median radiographical score 25.0) claimed to be predominantly in good spirits, while those with clinically and radiographically more severely damaged joints (median clinical score 24.0 and median radiographical score 36.0) suffered markedly from depressive spells. According to the Mann–Whitney U-test, this discrepancy was found to be significant ($P = 0.031$).

Of our haemophiliacs 28/79 (35.4%) had been on sick leave from work more than twice in 1999 or were prematurely retired as a result of their joint pain. These patients showed a significantly higher clinical ($P = 0.001$) and radiographical ($P = 0.003$) joint score (median clinical score 30.5 and median radiographical score 43.0) than those patients who regularly attended work (median clinical score 17.0 and median radiographical score 26.0). Patients who had prematurely retired from work were found to have all six joints damaged (clinical and radiographical median of 6.0 damaged joints), thereby on average having two more joints severely damaged than those patients who were still able to work (clinical and radiographical median of 4.0 damaged joints).

**Discussion**

**Subjective vs. objective measurements**

In general, it should be mentioned that clinical score and questionnaire are not validated. The Pettersson Score is validated but this does not seem to have an influence on the clinical outcome: only clinical and radiological scores > 2 points are associated with pain. For the knee joint the correlation between subjective pain score (VAS) and clinical evaluation between subjective pain score (VAS) and radiographical findings showed a clear association. Although not as pronounced, an association between clinical results and subjective pain score (VAS) was also found for the right ankle. In these joints the treating physician can therefore deduce that with increased radiographical damage and clinical impairment the patient will suffer increased joint pain. Why this relationship is particularly manifest for the right knee remains speculative.

Our results underline the findings of Erlemann and Wörtler [15] that the haemophiliac experiences his arthritic joint as particularly painful, far more than he is troubled by a damaged ankle. This may be explained by the larger range of motion of the knee joint as well as that in the knee motion is primarily controlled by muscles and ligaments. The ankle has the highest density of receptors of all human joints. Initial motion and load induction occur here. Minor false movements and increased stress are usually completely absorbed by the healthy ankle, with the effect that excess strain is taken from neighbouring joints [16].

In parallel to our findings, Aznar et al. [5] and Erlemann et al. [17] found the ankle to be radiographically the most damaged joint in the haemophiliac. This is attributed to the increase of daily life and sporting activities made possible by the massive progress in factor substitution therapy [13]. The result is that injury-induced bleeding into the ankle joint occurs more frequently. While a less severe bleeding episode into the knee joint will usually cause significant pain and subsequent immobilization, this is often not the case with minor bleeding into the ankle joint, where the patient may continue to weight-bear [15]. The ensuing minor inflammatory reactions, which may subjectively go unnoticed, are considered particularly damaging for the joint and may explain why the ankle is most frequently and most severely arthropathically afflicted [18]. With the ankle joint playing such a key part in estimating the severity of haemophilic arthropathy, it seems all the more important to point out that patients considered modified orthopaedic shoes to have an important role in reducing pain. The effect of the shoe is chiefly on the ankle joint in that the foot and ankle are stabilized and strain and impact absorbed.

**Parameter ‘daily activities’ in other studies**

In so far as one can compare this study to others, Miners et al. [8] also found a highly negative correlation between the parameter ‘physical functioning’ and the intensity of ‘bodily pain’ in haemophiliacs. However, in Miners et al.’s study the value of this comparison was diminished because the two criteria were evaluated solely by means of a patient questionnaire, thereby representing only the subjectively flawed patient standpoint. Solovieva [11] mentions the association between the degree of invalidity and the pain status measured by VAS, whereby the more pronounced the invalidity, the more intense the pain is claimed to be. Solovieva asked patients to determine their level of invalidity on a 5-point scale, with an increase in points suggesting an increased restriction of the haemophiliac’s bodily activity. In a sense, this level of invalidity reflects the clinical impairment of patients and, in analogy to our results, correlates positively with their pain status.

There is a tendency that with increased clinical and radiographical patient scores an augmented restriction of the haemophilic’s quality of life can be found; an aspect that has been highlighted in numerous studies [5,7–9,11]. Every second patient questioned could not adequately curb joint pain despite the use of factor concentrates, NSAIDs, modified orthopaedic shoes, ointments, stabilizing bandages or cortisone, and almost one-third of patients regularly taking oral analgesic drugs claimed that pain relief was insufficient. This calls for more efficient methods to combat the pain of haemophilic arthropathy. Apart from the optimization of drug therapy, a further solution could be cognitive behavioural therapy. Some studies [19–21] have revealed the positive effect of this psychological approach on the management of arthritic pain. Whether this management option is practicable will have to be shown in larger surveys.
Conclusions

The aim of this study was to determine to what extent the haemophiliac's subjective impairment resulting from arthropathies correlated with objective clinical and radiographical parameters. We found a significant association between pain intensity and clinically and radiographically verified joint damage for both knees and for the right ankle. The number of painful joints correlated well with the amount of clinically/radiographically affected joints.

Older haemophilic patients in particular suffer chronic pain. Depending on the affected joint, the more pronounced the objectively assessed joint damage in patients with haemophilia, the higher the subjectively claimed joint pain and loss of quality of life that can be expected. This statement is limited in so far as that in this study statistically significant correlations were only found for the knee and ankle joints. Our results underline that the treatment of painful symptoms from arthropathies is frequently insufficient. Scores and questionnaires may help to adequately define the haemophiliac's pain status, thereby offering the possibility of assessment and long-term observation.

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