Joint Surgery in the Adult Patient with Hemophilia

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ISBN 978-3-319-10779-0 ISBN 978-3-319-10780-6 (eBook)
DOI 10.1007/978-3-319-10780-6
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014954442

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

A reminiscence of an elective orthopaedic repair performed in San Francisco in the early 1960s suggested that in the pre-concentrate era, surgical operations were performed only to try and save a life, and if the patient survived, the postoperative course was stormy and lengthy. In 1968, Dr. J. Vernon Luck, Sr., did succeed in inserting a vitallium cup into a patient's damaged acetabulum under cover of the newly available factor VIII concentrate. Although the patient subsequently did very well with a Charnley 'total' hip replacement, he died of AIDS in 1988 [1].

This early report shows the importance of the collaboration needed between the haematologist and the orthopaedic surgeon in order to provide good haemostasis during joint surgery in haemophilia. Almost half a century later, this book reviews the tremendous advances that have been made in such surgery. The use of continuous infusion and recombinant products has allowed for results similar to those in the general population [2]. These issues are addressed in Chap. 2.

The knee is the most common joint to be affected in haemophilia, followed by the elbow, ankle, hip and shoulder [3]. All these joints are considered in Chaps. 5, 6, 7, 8 and 9 in this book. Total knee replacement provides the most extensive experience and is reviewed in Chap. 8 by the editor of this book, Carlos Rodriguez-Merchán, a surgeon with enormous experience in haemophilic patients.

Although radiography has a place in the management of joint disease in haemophilia, the use of other imaging modalities has revolutionized therapeutic decision making, with magnetic resonance imaging and ultrasonography in particular coming to play an important role. Imaging, reviewed in Chap. 4, is now essential for the good management of joint disease including surgery.

Thrombo-prophylaxis remains a contentious issue for patients with an inherited bleeding disorder, and this is discussed in Chap. 11. There is no doubt that the management of haemophilia requires a multidisciplinary team approach including the physiotherapist and the rehabilitation specialist. These important aspects of care are covered in Chap. 12.

Pain relief for haemophilic individuals with arthropathy can be problematical in the face of the many analgesics exhibiting anti-platelet effects. Inclusion of Chaps. 13 and 14 is therefore very relevant. It is interesting to note that in the 1968 experience, narcotics were given in high doses, and these could be tapered quickly following joint replacement and pain relief [1].

It was Inga Marie Nilsson from Malmö, Sweden, who pioneered prophylaxis in the 1960s, and there is now widespread acceptance of this as a 'state-of-the-art' treatment in the well-resourced world following the publication of two random controlled trials [4]. However cost-effectiveness remains an issue, and a discussion of this is included in Chap. 15.

The advent of safe clotting factor concentrates together with the widespread use of prophylaxis raised the prospect of a generation of patients with haemophilia who would not have joint disease. It was even thought that the orthopaedic surgeon would be redundant in this group of patients. Clearly, as this book attests, that is not the case. Patients with haemophilia are living much longer and approaching a normal life expectancy, and this holds true even for those with HIV infection. Many of these patients have severe arthropathy because in their younger life, treatment was unavailable or inadequate. Although modern recombinant products are safe from transfusion-transmitted disease, inhibitors remain a challenge, and these patients may develop arthropathy through ineffective treatment. Those who have had the benefit of modern treatment and prophylaxis demand a normal lifestyle – young boys play football and the ankle will remain a challenging joint. Furthermore, this book addresses the well-resourced world: many parts of the world can only dream of joint surgery.

Much has been achieved in the last 50 years, but the orthopaedic surgeon is likely to be required in the comprehensive care team for many years to come. This book will help those providing the essential joint surgery.

London, UK

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MA, MD, DSc(Med), FRCP, FRCPath, FRCOG

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Contents

Musculoskeletal Manifestations of Hemophilia

1

E. Carlos Rodríguez-Merchán and
Hortensia De la Corte-García

1.1 Introduction

In patients with hemophilia, orthopedic (musculoskeletal) problems can affect the joints or the muscles [1–3]. Virtually 90 %, however, involve the joints and they normally begin in childhood. Hemarthroses (bleeding into the joints) tend to recur in spite of the synovial membrane's capacity to reabsorb the blood. When there is a lot of blood in the joint, the synovial membrane becomes hypertrophied because the cytokines and angiogenic factors from the intra-articular hemorrhage stimulate the synovial cells to replicate [3]. Then, the hypertrophic synovium is more prone to bleed again (it becomes very friable and hypervascularized), ending up in a vicious circle of hemarthrosis-synovitis-hemarthrosis. In addition, the blood in the joint can directly cause death of the chondrocytes in the joint cartilage [3].

The joint pain caused by the above processes can lead to an antalgic flexion deformity of the affected joint which is initially reversible, but will eventually become permanent (fixed deformity) (Fig. 1.1). The hyperemic reaction caused by the hemarthrosis leads to asymmetrical hypertrophy of the epiphyseal growth plates which can go on to result in axial deviation of the affected limbs. This all leads to joint damage, which progresses within only a few years to destruction of the joint (hemophilic arthropathy) (Fig. 1.2) [4].

The non-joint-related musculoskeletal problems in hemophilia, which account for over 10 % of orthopedic lesions in the patient with hemophilia, are essentially soft-tissue hematomas, muscle hematomas, and pseudotumors [4].

With adequate prophylaxis, at least from the age of 2–18 (ideally lifelong), it is possible to convert severe hemophilia into a moderate condition, considerably reducing (although not totally preventing) the associated musculoskeletal problems [5–7].

The main benefit of orthopedic surgery in hemophilia is that it markedly improves the patient's quality of life [8]. This is achieved by appropriately managing the joint problems (hemophilic arthropathy) and the muscle hematomas and their complications (hemophilic pseudotumors, nerve paralysis caused by compression, and compartment syndrome) [7].

The level of evidence of hemophilia literature is very low. In fact, no study on the musculoskeletal complications of hemophilia has been included in the Cochrane Library so far. The aim of this chapter is to discuss the management of the musculoskeletal manifestations of hemophilia.

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_1,

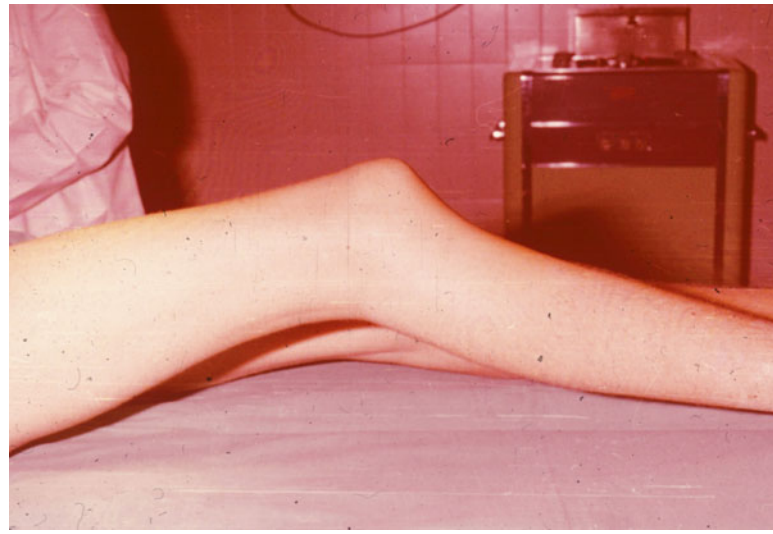

Fig. 1.1 Irreversible flexion contracture of the knee, secondary to multiple hemarthroses. Note the posterior subluxation of the tibia associated with the problem

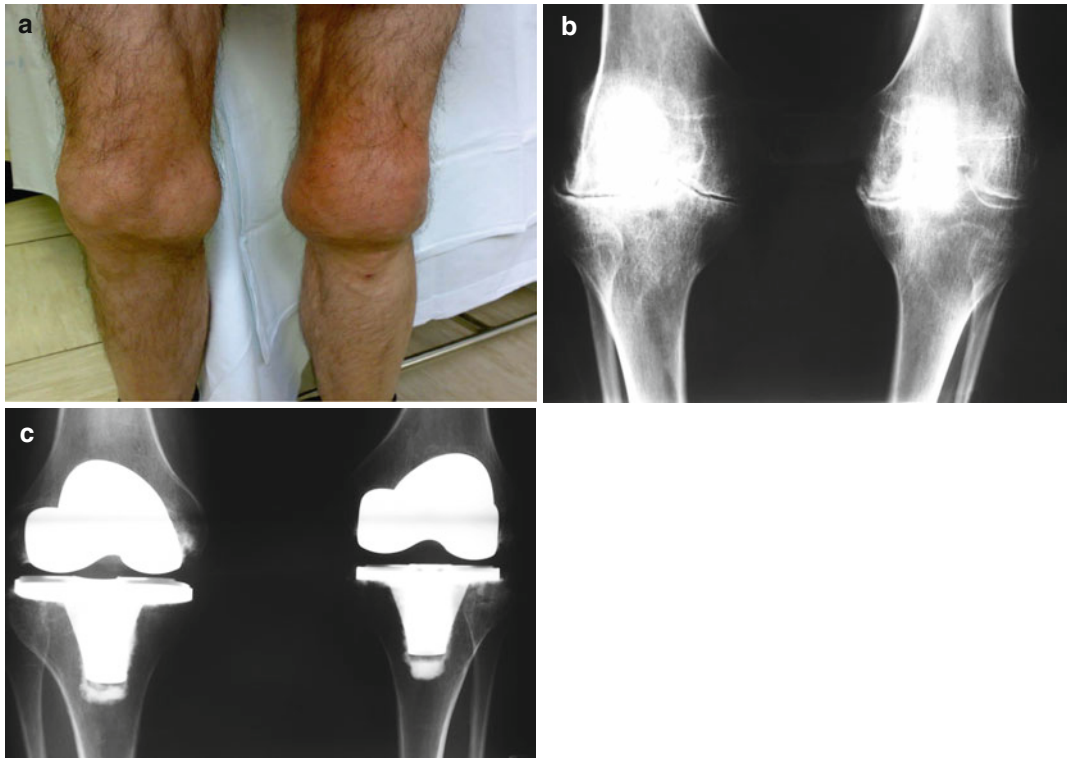

Fig. 1.2 Clinical appearance of severe hemophilic arthropathy in both knees (**a**) and the radiographic images confirming the joint disease (**b**). A bilateral total knee replacement was performed in two stages, with a satisfactory result (**c**)

1.2 Management of Muscle Hematomas and Their Complications

1.2.1 Compartment Syndrome and Compression Neuropathy

Muscle hematomas can occur in any part of the body (Fig. 1.3) although the most common sites are the iliopsoas muscle and the flexor compartment of the forearm [4, 9]. If not adequately dealt with, they can lead to compartment syndrome and a possible need for urgent surgical decompression of the compartment [10]. Iliopsoas hematomas are often associated with paralysis of the crural nerve. It is important to remember that a right iliopsoas hematoma can be confused with appendicitis. The diagnosis of iliopsoas hematoma should be confirmed by ultrasound and/or computed tomography (CT). Crural nerve paralysis often requires rehabilitation for as long as 18 months before it fully resolves. Electromyography (EMG) is useful for the diagnosis and for assessing progress. Periodic ultrasounds are essential to confirm that the hematomas have been completely reabsorbed, and with the appropriate hematological treatment, this does usually occur. New bleeding, however, is common, and the treatment must therefore be continued for several weeks or even months until complete reabsorption is certain. Surgical decompression of the compartment is not appropriate for an iliopsoas bleed even if there is crural nerve involvement.

In the forearm, surgical opening of the entire flexor compartment may be necessary, since once compartment syndrome is established, it has a considerable effect on the function of the whole arm [4]. In some patients (particularly the immunosuppressed), a soft tissue hematoma can become spontaneously infected and turn into an abscess. Diagnosed early, this can generally be resolved with treatment based on intravenous antibiotics and surgical drainage.

1.2.2 Hemophilic Pseudotumors

Although rare, pseudotumors are a serious complication of hemophilia. They are progressive cyst-like inflammations that affect the muscles, caused by recurrent bleeding and associated with radiographic evidence of bone involvement [11–13]. Most pseudotumors are seen in adult patients and occur near the proximal ends of the long bones. However, they can occur distally in the wrist and ankle in young patients before skeletal

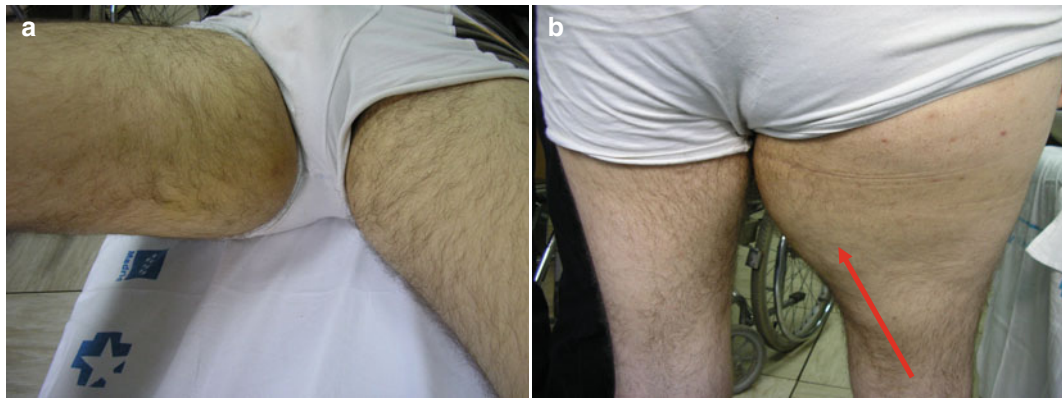

Fig. 1.3 Large hematoma in the right thigh of a hemophilia patient, anterior view (**a**) and posterior view (*arrow*) (**b**).

maturity. If left untreated, proximal pseudotumors may destroy the soft tissues, erode the bone, and cause serious vascular and/or nerve damage.

Despite having a mortality rate of 20 %, the treatment of choice for proximal pseudotumors is surgical removal [11]. This mortality is primarily due to surgery. Regression, although not true cure, has been reported with long-term treatment with the deficient clotting factor and immobilization. This treatment should only be used in inoperable cases, such as patients with inhibitors who are poorly controlled. Percutaneous evacuation of the pseudotumor followed by filling with fibrin glue and/or cancellous bone can at times provide satisfactory results. Preoperative embolization of large pelvic pseudotumors may help to reduce intraoperative bleeding when removing surgically.

Distal pseudotumors can be controlled with hematological treatment and immobilization. It is important to be aware of the possibility of pseudotumors when one or more masses are detected in the limbs or pelvic region of a person with hemophilia. However, chondrosarcoma and liposarcoma have been confused with hemophilic pseudotumors in these patients [14]. Ultrasound, CT, and MRI (magnetic resonance imaging) will help to confirm the diagnosis in each case.

1.3 Management of Hemophilic Arthropathy

Hemophilic arthropathy is polyarticular (knees, ankles, elbows, hips, shoulders) and affects the patients from early childhood. Hemarthroses are accompanied by severe pain and an initially reversible antalgic flexion contracture. The blood within the joint alters chondrocyte (cartilage cells) proteoglycan synthesis, causing their death (apoptosis).

1.3.1 Hemarthrosis

Proper treatment of hemarthrosis should include early diagnosis, adequate hematological treatment, evacuation of the blood in the joint (arthrocentesis), physiotherapy, and prevention of new episodes of bleeding [7]. Clinical diagnosis should be confirmed by ultrasound. X-rays should also be performed to rule out (or confirm) radiological signs of joint disease.

A great deal of debate continues to surround the subject of joint aspiration (evacuation of the hemarthrosis or arthrocentesis) in hemophilia. Until very recently, it was considered to be extremely dangerous due to the high risk of new bleeding and infection (septic arthritis). My view is that major hemarthroses must be aggressively treated to prevent progression to synovitis and recurrent joint bleeds. However, there is no evidence of grade I in the literature confirming the role of arthrocentesis in the setting of hemarthrosis. The use of joint aspiration is more a matter of experience based in empirical data [4]. Therefore, we use arthrocentesis in acute and tense hemarthroses. The joint puncture must be done under tight hematological control and strict aseptic conditions [4].

Following arthrocentesis, it is recommended that the joint be immobilized for 3–5 days with a compression bandage. Ice should not be used for acute hemarthroses, as that seems controversial now [15]. The patient should then undergo a course of controlled physiotherapy, as rehabilitation is essential in order to prevent, as far as possible, chronic synovitis. The duration of the physiotherapy will depend on the time required for full recovery of joint mobility and muscle strength. Recurrent bleeding episodes must be avoided during the recovery period. Patients should be seen every 3 months in order to assess their progress closely.

1.3.2 Synovitis

Another problem is synovitis (synovial hypertrophy), caused by the cytokines and angiogenic factors from the intra-articular hemorrhage that stimulate the synovial cells to replicate, which eventually leads to a vicious circle of hemarthrosis-synovitis-hemarthrosis [3]. The circle must be broken by synovectomy. This may be medical or surgical. Medically, the best type is radiosynovectomy, the alternative being

chemical synovectomy. Surgical synovectomy can be performed arthroscopically or by open surgery [16–20].

Short courses of intra-articular prednisone should be taken into account as an option prior to synovectomy [21].

Review of literature prior to 2002 showed no reports of malignancy related to ^{32}P [22, 23]. However, in 2002 and 2009 two cases of acute lymphocytic leukemia (ALL) were reported after radiosynovectomy in two hemophilic children [23]. Given the short latency between exposure and diagnosis of ALL in both patients, the casual relationship between ^{32}P exposure and ALL could not be firmly established. It is important to note, however, that there was also insufficient data to rule out causality.

Recently, a report of Infante-Rivard et al. demonstrated that there was no dose-response relationship with the amount of radioisotope administered or the number of radiosynovectomy treatments [19]. The study provided some indication for the safety of the procedure, but homogenous diagnostic groups of younger patients (such as hemophilic patients) receiving radiosynovectomy will need more evaluation.

The principal aim in hemophilia is, as far as possible, to prevent hemarthrosis before the synovitis can occur. Once developed, the aim is to treat it as early and aggressively as possible. The diagnosis should be confirmed by ultrasound or MRI (magnetic resonance imaging). Ultrasound is particularly useful for the knee, while MRI is more accurate for the elbow and the ankle. Nowadays power Doppler ultrasonography (US) is a very important tool for assessing knee bleeds [24, 25]. When conservative treatment, i.e., deficient clotting factor replacement therapy plus physiotherapy, fails to break the hemarthrosis-synovitis-hemarthrosis vicious circle, intervention is required to destroy the synovial membrane.

A medical synovectomy is simply the injection of a substance into the joint to "stabilize" the synovial membrane. The main reason for performing any type of synovectomy is the presence of an excessive amount of synovial membrane in a particular joint (hemophilic synovitis). We consider medical synovectomy the procedure of choice in cases of hemophilic synovitis with recurrent hemarthrosis, and that surgical synovectomy should only be used in cases where medical synovectomy has repeatedly failed. In view of its efficacy and minimal risk, medical synovectomy may also be used in patients with inhibitors [13, 14, 26].

The differential diagnosis between synovitis and hemarthrosis can, and should, be made by US and/or MRI. Plain X-rays are useful for assessing the degree of joint disease when deciding on synovectomy. It is logical to expect that the worse the synovitis, the more difficult it will be to resolve it by synovectomy. Indeed, in severe cases, multiple consecutive medical synovectomies can be necessary, and even then, surgical synovectomy may still be required.

The main indication for medical synovectomy is the presence of chronic hemophilic hypertrophic synovitis causing recurrent hemarthroses that do not respond to hematological treatment. The most commonly used these days are chemical synovectomy (rifampicin, oxytetracycline) and isotopic synovectomy or radiosynovectomy (with yttrium-90, phosphorus-32, or rhenium-186). In general, medical synovectomy has a 70 % efficacy rate, and it can be used at any point in the patient's life; the main aim is to reduce the number and severity of hemarthroses and the damage the blood in the joint causes to the cartilage over the medium and long term.

Radiosynovectomy can be repeated if the first injection fails, up to three times at 6-month intervals if radioactive isotopes are used, or weekly, as many as 10–15 times if using rifampicin or oxytetracycline. Radiosynovectomy has been used worldwide for over 40 years, and no evidence has been found of any harm caused by the radioactive isotopes [27, 28]. In my opinion, assuming the isotopes are available, radiosynovectomy (with yttrium for knees and rhenium for elbows and ankles) is the procedure of choice in children aged over 12. We prefer rhenium for elbows and ankles because its therapeutic penetration power (1 mm) correlates well with the size of the synovium of medium-sized joints. However, in the knee we prefer yttrium because its therapeutic penetration power is 2.8 mm and it correlates

well with the size of the knee synovium. Failing radiosynovectomy, rifampicin, and oxytetracycline are the alternatives (multiple, fairly painful, weekly injections are required for effective chemical synovectomy) [16–20].

Surgical synovectomy can be performed by open surgery or by arthroscopy. Most authors recommend arthroscopy [20, 29]. Once skeletal maturity has been reached, open surgery synovectomy may be indicated for the elbow, combined with resection of the radial head to improve pronation and supination of the elbow. In our center, we now always opt for radiosynovectomy with yttrium-90 (knees) or rhenium-186 (elbows and ankles) as the first option, and then if, after 2–3 radiosynovectomies at 6-month intervals, we have not managed to control the synovitis, we turn to surgical synovectomy (preferably arthroscopic) [26]. Prior radiosynovectomy does not lessen the chance for optimal response with surgical synovectomy (radiation does not cause fibrosis that makes complete resection difficult).

In terms of radiosynovectomy, our experience has confirmed a 70 % reduction in the mean rate of bleeds. Regarding pain and ROM, the rate of improvement is 70 % (statistically significant) and 3 % (not significant), respectively [18]. We use yttrium-90 (185 MBq, TPP-therapeutic penetration power of 2.8 mm) in the knees and rhenium-186 (TPP 1 mm) in the elbows (56–74 MBq) and ankles (74 Mbq). We have given over 400 injections to date (1–3 per patient, at 6-month intervals). The risk of complications is 1.5 % (four inflammatory responses, one mild radiation burn to the skin, one septic arthritis of the knee). Radiosynovectomy is our first option for the treatment of synovitis (450 euros per injection), with arthroscopic synovectomy as second-line treatment (4,500 euros). We opt for arthroscopic synovectomy after the failure of three attempts at radiosynovectomy at 6-month intervals. So far, only 3.5 % of patients have required this technique [18].

1.3.3 Advanced Joint Disease

The literature seems to support the use of the intra-articular injections of hyaluronic acid (so-called viscosupplementation) in the treatment of knee osteoarthritis, because it diminishes pain and improves disability, generally within 1 week and for up to 3–12 months (but especially at the 5–13-week postinjection period). There are only five reports in the literature on the efficacy of knee viscosupplementation in hemophilia, all of them with a low level of evidence [30]. The five studies dealing with viscosupplementation in hemophilia recommend it for hemophilic arthropathy of the knee as a way of delaying the need of operative treatment when noninvasive medical therapy (relative rest, oral anti-inflammatory drugs, oral analgesics, and physical therapy) has failed. My view is that the short-lived improvement afforded by viscosupplementation does not seem to warrant its use in hemophilic patients given the risks and the cost involved. Further trials are required to ascertain whether viscosupplementation should be indicated in painful radiological hemophilic arthropathy of the knee [30].

When the extent of joint involvement progresses as a result of the joint bleeds being impossible to control, patients will not only develop certain joint deformities and contractures but also subchondral cysts and osteophytes. Valgus deformity of the knee and the ankle is common, while the most typical in the elbow is hypertrophy of the radial head. Hemophilia patients may therefore present with valgus flexion deformities in one or both knees, equinus (Fig. 1.4) in one or both ankles, and in one or both elbows in flexion. Osteotomy is often necessary on the knee and ankle to correct the poor joint alignment [31].

Flexion contractures are common in hemophilia and difficult to resolve once they become fixed. The joints most affected are the elbows, knees, and ankles. The contracture is initially antalgic and is related to a hemarthrosis, which means that within the first few weeks, the contracture can be resolved with the appropriate treatment (hematological treatment plus rehabilitation) [32]. The deformity will subsequently become fixed, with the resulting negative effects on function, and may even require surgery. In the knee, lengthening of the tendons in the popliteal fossa (hamstrings release) combined with a posterior capsulotomy or supracondylar extension osteotomy may correct the flexion deformity. In

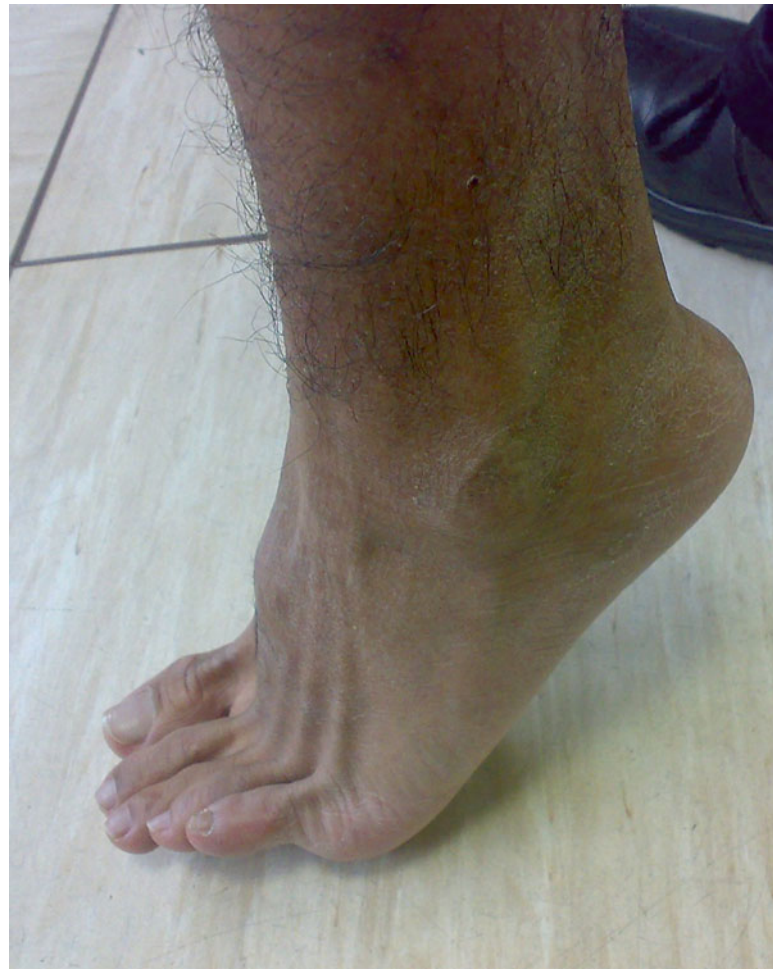

Fig. 1.4 Severe equinus deformity of the ankle in a patient with hemophilia

the ankle, Z-lengthening of the Achilles tendon may also be necessary [4].

In the hip, patients may develop a disease similar to Perthes disease in relation to the recurrent joint bleeds. Perthes is a condition in children characterized by a temporary loss of blood supply to the hip. Without an adequate blood supply, the rounded head of the femur dies. The area becomes intensely inflamed and irritated. Perthes is really a complex process of stages. Treatment of Perthes may require periods of immobilization or limitations on usual activities. The long-term prognosis is good in most cases. After 18 months to 2 years of treatment, most children return to normal activities without major limitations. Perthes disease usually is seen in children between 4 years and 10 years of age. It is five times more common in boys than in girls. Initial treatment is with an abduction orthosis, thereby making surgery rarely necessary (varus osteotomy of neck of the femur). Juxta-articular cysts are also common and, when large and symptomatic, may require curettage and filling with bone graft, with or without fibrin glue. The formation of large anterior osteophytes is common in the ankle, and when symptomatic, surgical excision may be necessary.

Many hemophilia patients under the age of 40, and as young as 10, already have severe joint damage (advanced joint disease). At this point, the possible treatments are radial head resection, total hip replacement, arthroscopic debridement of the knee, total knee replacement (TKR), and ankle arthrodesis [4]. When there is multiple joint involvement, operating on only one joint may not improve the patient's overall function-

ing, and our objective should therefore be to achieve one functional limb. It is recommended in hemophilia that multiple joint interventions be done in one single operation, since the complication rate is lower than would be expected and the rehabilitation time after multiple-joint surgery is relatively short [33].

In the elbow, radial head resection tends to reduce the number of joint bleeds and improve the degree of pronation and supination. Elbow deformity can cause ulnar nerve damage, which may require surgical neurolysis (release) [34, 35].

In the hip, the best solution is total hip replacement (THR). A spontaneously ankylosed hip can even be converted into a prosthesis, with the aim of improving the severe low back and knee pain suffered by patients with an ankylosed hip [36, 37].

In the knees, if the patient is very young and has a long life expectancy, it may be worthwhile debriding arthroscopically in order to relieve the pain for a few years [38]. If the arthroscopic knee debridement fails, TKR may be an option [39–47]. THR and TKR appear to last longer in people with hemophilia than in people of a similar age with osteoarthritis [45]. It is evident that in the age of joint replacement, hip and knee replacement should be offered to the hemophilia patient with massive joint damage associated with severe pain and marked functional disability. Nonetheless, the surgeon and the patient must weigh up the risks and benefits (especially if the patient is severely immunosuppressed).

THR and TKR have a limited span of use due to wear and tear (15 years for knees, 20 years for hips). Ideally, the youngest age joint replacement can be done without having to replace it later is 60 for THR and 65 for TKR. Our preferred type/brand of prosthesis for the knee is a posterior stabilized (PS) design with cemented components (with antibiotic-loaded cement), always with patellar resurfacing (Insall-Burstein type). For the hip we prefer a cemented Charnley design.

The risk of infection is higher for hemophilia patients undergoing total joint replacement, with a mean risk of approximately 7 % [48], than in the non-hemophilia population, where this figure is only 1–2 %. One of the risks inherent with joint replacement in the hemophilic patient is risk of Staphylococcus infection from central venous catheters (CVCs). To reduce that risk systematic preoperative screening by swab is very important. Prevention of positive cases by means of nasal decontamination (mupirocin 3 days) is advisable. Preoperative antibiotic prophylaxis has shown itself to be an efficient method to lower infection rates. Operating theaters ideally should be equipped with laminar flow [49]. In persons with hemophilia, there are three additional risk factors: insufficient hemostasis, HIV-positive status, and central venous catheters (CVCs). Implementing the preventive measures for the general population and a sufficient level of clotting factor for 2–3 weeks can help diminish the infection in persons with hemophilia undergoing TKR. In HIV-positive patients with CD4 count less than 200 cells/μl, early, vigorous treatment should be instituted for suspected infection and surgical intervention individualized based on the balance of risks and benefits. Strict adherence to hand washing and aseptic technique are essential elements of catheter care. Caregiver education is an integral part of CVC use, and the procedural practices of users should be regularly reassessed [49]. On the other hand, continuous infusion (CI) of factor is preferable to bolus infusion (BI) to reduce bleed risk which we know can be associated with higher infection risk.

The standard treatment for end-stage osteoarthritis of the ankle joint in hemophilic patients has been fusion of the ankle joint [50]. Total ankle replacement (TAR) is still controversial as a treatment option. Barg et al. [51] analyzed 10 total ankle replacements performed in eight hemophilia patients. Their mean age was 43 years and the average follow-up was 2.7 years. They stated that for patients with hemophilic osteoarthritis of the ankle joint, TAR is a valuable alternative treatment to ankle fusion.

1.4 Potential Complications of Treatment

The main risks of orthopedic surgery in hemophilia are infection and bleeding [4]. The mean risk of TKR infection is 7 %, as opposed to 1–2 %

in the osteoarthritis population. Two operations are generally necessary (two-stage revision arthroplasty) to solve it (with an 85–90 % likelihood of success). Many hemophilia patients are infected with HIV (human immunodeficiency virus) and HCV (hepatitis C virus). HIV infection can increase the risk of postoperative infection. In HIV-positive persons with hemophilia with CD4 count less than 200 cells/μl, early, vigorous treatment should be implemented for suspected infection and surgical orthopedic intervention individualized based on the balance of risks and benefits [49]. What also must be remembered is the risk of HIV and HCV infection for the "surgical team" in the event of accidental puncture wounds.

Excessive postoperative bleeding can be the result of inadequate hemostasis or the development of a pseudoaneurysm during the intervention, which usually becomes evident in the immediate postoperative period (sooner or later). After ruling out a problem with hemostasis (that the levels of clotting factor are not too low), the diagnosis of pseudoaneurysm must be confirmed by CT angiogram or conventional angiogram. Embolization of the artery is the first treatment option, and artery ligation (with or without distal bypass) is the next alternative (open surgery). Early diagnosis and treatment of this complication is essential, in particular to prevent the risk of infection of the associated excess blood in the joint. It appears that pseudoaneurysms do not develop more commonly in hemophiliac arthroplasties than in non-hemophiliac arthroplasties [52].

In orthopedic surgery for hemophilia patients, general anesthesia is recommended, since spinal anesthesia can lead to serious complications (deriving from development of a spinal hematoma) [53].

In patients with inhibitor (antibody to the clotting factor given by intravenous infusion), hemostasis can be achieved using bypassing agents such as aPCCs (FEIBA: factor VIII inhibitor bypassing agent, Baxter) and rFVIIa (recombinant activated factor VII, NovoSeven, Novo Nordisk) [54–58]. However, if surgical management of inhibitor patients is made, we should outweigh the risks and the advantages of surgery. In other words, given the high risk of bleeding complications and need to resort to rescue therapy, surgery in patients with inhibitors is not to be undertaken lightly.

The risk of venous thromboembolism (VTE) after orthopedic surgery in hemophilia patients is very low [59]. In fact, little has been published addressing the role of thromboembolic prophylaxis in the hemophilic patient population following THR and TKR. Although the American College of Chest Physicians (ACCP) and the American Academy of Orthopedic Surgeons (AAOS) have set guidelines for thromboembolic prophylaxis in the general population, no such standard of care is in place for hemophilic patients. While the risk of thrombosis in hemophilic patients following THR and TKR is thought to be lower, cases have been reported of pulmonary embolism and deep vein thrombosis (DVT) in hemophilic patients [59]. In our center we do not use pharmacological prophylaxis of VTE in persons with hemophilia. In fact, we have never seen such complication in patients with hemophilia so far. However, in non-hemophilia patients we use daily subcutaneous low-molecular-weight heparin (LMWH) for 2 weeks after THR and TKR. In all patients we advise mechanical prophylaxis by means of early mobilization after surgery.

Most authors replace the deficient coagulation factor for 10–14 days. However, a high rate of infection has been reported when using insufficient hemostasis [46]. To achieve adequate hemostasis during major surgery, our recommendation in hemophilia A patients is to perform clotting factor replacement preoperatively until a minimum level of 100 % of normal is achieved; then the level is maintained at 60 % of normal for 14 postoperative days, and then clotting factor replacement is infused to obtain a level of 30 % of normal prior to rehabilitation sessions for 8–10 weeks.

The World Federation of Hemophilia (WFH) guidelines [60] endorsed by the International Society of Thrombosis and Hemostasis (ISTH) suggest that in hemophilia A patients undergoing major surgery, plasma factor peak level (when there is no significant resource constraint) must

be 80–100 (IU/dL) preoperatively. In the postoperative period such a level must be 60–80 in days 1–3, 40–60 in days 4–6, and 30–50 in days 7–14. In minor surgery, the desired level in hemophilia A must be 50–80 preoperatively. Postoperatively it must be 30–80 during days 1–5, depending on the type of procedure. In patients with hemophilia B undergoing major surgery, the preoperative recommended level is 60–80. In the postoperative period the level must be 40–60 in days 1–3, 30–50 in days 4–6, and 20–40 in days 7–14. In minor surgery the preoperative level in hemophilia B must be 50–80, while the postoperative level must be 30–80 in days 1–5, depending on the type of procedure.

Conclusions

A multidisciplinary team is essential if satisfactory results are to be obtained in orthopedic surgery in people with hemophilia. Prophylaxis with the deficient clotting factor from the age of 2 until the patient reaches 18 seems to be the only effective way to minimize the joint bleeding and joint deformities typical of hemophilia in adulthood (joint disease). Surgical interventions that are commonly required by hemophilia patients include joint aspiration (arthrocentesis), synovectomy (arthroscopic or radiosynovectomy), osteotomy, arthroscopic debridement, tendon lengthening, arthrodesis (fusing of joints), total joint replacements, resection or percutaneous treatment of pseudotumors, fasciotomy for compartment syndrome, arthrotomy for septic arthritis, drainage of infected hematomas (abscesses), and other orthopedic interventions. With the current hematological treatments, any of the aforementioned orthopedic surgical interventions can be carried out in people with hemophilia with a high degree of safety (although not as high as in patients without congenital clotting disorders). Orthopedic surgery in hemophilia patients tends to be complex and involves a higher risk of both bleeding and infection. With collaboration between hematologists, orthopedic surgeons, and other specialists, we can make a big difference in the quality of life of people with hemophilia. Good hemostasis, appropriate surgical technique, and good postoperative rehabilitation are essential.

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2 Hematological Concepts and Hematological Perioperative Treatment

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2.1 Introduction

Hemophilia A and B are X-linked recessive bleeding disorders caused by deficiency of factor VIII (FVIII) or factor IX (FIX), respectively [1]. Because of the mode of inheritance, hemophilia A and B mostly affect males, while females are carriers. Both factors take part in the intrinsic pathway of blood coagulation. Depending on the concentration of FVIII or FIX coagulant activity in blood, the disorders may be classified as severe (<1 % of normal activity), moderate (1–4 %), or mild (5–25 %) (Table 2.1). The prevalence of hemophilia A is 1 in 5,000 male live births, and that of hemophilia B is 1 in 30,000 [1]. The hallmarks of clinical symptoms of hemophilia are joint bleeds (hemarthroses) and muscle bleeds (muscle hematomas), bruising, and prolonged severe hemorrhage after surgery or trauma. The joints most commonly affected are knees, elbows, ankles, shoulders, and hips. Joint bleeding usually appears when the child starts to walk and without a known trauma [2].

Joint hemorrhage (hemarthrosis), without a correct treatment, predisposes to recurrent bleeds, chronic synovitis, and hemophilic arthropathy [3]. The main goal of replacement therapy is to prevent the development of this pathology. On-demand treatment has been shown to slow the progression of arthropathy, but cannot prevent it [4]. The need for primary prophylaxis to prevent joint disease was established in the studies of Nilsson et al. in Sweden [5]. After 25-year follow-up, they observed that full-dose prophylaxis started in the first few years of life in boys with severe hemophilia prevented recurrent joint bleeds and preserved an excellent musculoskeletal status [5, 6]. They also observed that joint deterioration was frequent because of progressive destruction of joints already affected before the start of prophylaxis. This finding indicated that treatment should begin at a very early age, before joints are affected. This proposal for so-called primary prophylaxis is currently the emerging standard of care for patients with hemophilia without inhibitor around the world [7].

In the past four decades, hemophilia has changed from a fatal disease to a disorder with a

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_2,

Table 2.1 Classification of hemophilia according to factor levels and the clinical pattern (bleeds)

Severity	Factor levels (FVIII/FIX) (%)	Clinical pattern
Severe	<1	Severe. Spontaneous
Moderate	1–4	Moderate. Severe in surgery
Mild	5–25	Mild. After surgery

safe and effective treatment available. The overall life expectancy of patients has dramatically increased in the last years [8]. Quality of life has also improved, mainly as a result of the different forms of prophylaxis. However, unfortunately, many adult patients still suffer from musculoskeletal complications such as chronic synovitis, fixed-joint flexion contractures, and hemophilic arthropathy. These complications result in the need for various surgical procedures such as arthrocentesis, synovectomies, and total joint arthroplasty [9]. Surgery in children is less common than in adults, because children do not have as many orthopedic complications. The most frequent surgical procedures in children with hemophilia are circumcision, dental procedures, insertion of a central venous access device (CVAD), and tonsillectomy [10].

2.2 Replacement Therapy for Orthopedic Procedures in Hemophilia

2.2.1 Optimal Level and Duration of Replacement Therapy

Surgery in patients with hemophilia carries a high risk of bleeding and represents one of the most challenging areas in hemophilia care. Most surgical and invasive procedures can be performed safely in patients with hemophilia with factor replacement therapy (intravenous infusion of the deficient factor at the appropriate dose during the adequate period of time). Despite the risk, the results of orthopedic surgery in patients with hemophilia are good; however, a favorable outcome depends on coordination between multidisciplinary team members. It is also crucial to ensure that orthopedic procedures in hemophilia patients are conducted in specialized centers by an experienced team [11].

The optimal level and duration of replacement therapy needed to prevent bleeding complications have not been established yet. Hermans et al., on behalf of the European Hemophilia Therapy Standardization Board, published a review article about replacement therapy for invasive procedures in patients with hemophilia [12]. They reviewed 35 clinical studies regarding replacement therapy for major invasive procedures. The preoperative target factor levels for hemophilia A and B were in the majority of studies (26/31) aimed at values >80 %. In the 27 studies that addressed postoperative trough levels for the first week, values were >70 % in eight studies, >50 % in 11, and >20–30 % in eight. For the second week, data were available in 18 studies, and levels were >50 % in four, >30 % in seven, and >10–20 % in seven.

Duration of treatment in 31 studies varied from 5 to 14 days in 19 of the studies, 15–21 days in six, and up to 28 days or longer in further six studies. Bleeding complications occurred in 131/1,328 or 10 % of major surgical procedures, most of them in the papers published before 1990.

As part of this comprehensive task, Hermans et al. also performed a survey in 26 European Hemophilia Comprehensive Care Centers, representing 15 different countries to develop consensus recommendations for replacement therapy [12]. All centers prior to major orthopedic surgery reported a target factor level of at least 80 %. In contrast to the literature, continuous infusion (CI) was used in procedures performed in nearly half of the centers. In most centers, factor levels were maintained above 80 % in the postoperative period. With bolus infusion (BI), two infusions per day were administered in order to maintain trough levels above 80 % during the immediate postoperative period (from day 1 to 5) and around 60 % in the late postoperative period (from day 6 to 14) – values that are higher than published targets. The duration of postoperative replacement therapy ranged from 12 to 14 days. When CI was used, the factor level was maintained at 80 %

during the first five postoperative days and decreased to 30–40 % or 50–60 % between days 6 and 14. Before major orthopedic surgery, preoperative pharmacokinetic evaluation was performed in one-third of the centers and the recovery measured in more than half of them. Thromboprophylaxis with low-molecular-weight heparin was used in more than half, and antifibrinolytic treatment in more than two-thirds, of the centers [12].

Regarding synovectomy, Hermans et al. found four papers [12]. These four studies involved 158 patients undergoing 197 different procedures. Factor replacement always included a loading dose, ranging from 15 to 50 IU/kg in patients with hemophilia A and from 30 to 90 IU/kg in patients with hemophilia B, aiming at factor levels between 30–100 % and 30–90 %, respectively. Subsequent replacement therapy was either short (repeated bolus at full dose 8–12 h later and at half dose on day 2) or prolonged for 8 weeks using a prophylactic regimen (20 IU/kg three times per week – 2 weeks and 15 IU/kg two times per week – 6 weeks for hemophilia A and 30 IU/kg three times per week – 2 weeks and 25 IU/kg two times per week – 6 weeks for hemophilia B). No bleeding complications were reported. The survey from European Hemophilia Comprehensive Care Centers concluded that a target level of factor VIII (FVIII) between 80 % and 100 % was reported by 87.5 % of the centers. CI for this procedure was considered as an option by 62.5 % of the treaters. Treatment was continued for more than 7 days in a majority of the centers. Antifibrinolytics were used in 56 % of the centers. Our protocol for hemostatic cover in orthopedic surgery is shown in table 2.2.

In conclusion, in major orthopedic surgery the preoperative factor levels should be 80–100 %, and in the postoperative period the minimal factor level should be above 50 % in the first week and 30 % in the late postoperative period. Nevertheless, the World Federation of Hemophilia (WFH) guidelines for perioperative plasma factor VIII levels recommend a preoperative level of 120 %, tapering down to 50 % at 14 days. In addition, a very interesting report from Wong et al. supports the fact that maintaining a high level of clotting factor replacement therapy (at least 80 % factor replacement over the first two postoperative weeks) throughout wound healing can result in lower infection rates, comparable to that of total knee arthroplasty (TKA) in patients without hemophilia [13].

Table 2.2 Factor level for invasive orthopedic procedures at our center

Procedure	Preoperative factor level (%)	Postoperative factor level
Major orthopedic surgery	80–100	>80 % 1–7 days >50 % 8–15 days
Surgical arthroscopic synovectomy	80–100	>50 % 1–7 days
Radiosynovectomy	80–100	>50 % 1–5 days

2.2.2 Bolus Infusion (BI) and Continuous Infusion (CI) of Factor Concentrates

Most hemophilia centers use bolus infusion (BI) to replace coagulation factors for surgery [14]. Continuous infusion (CI) therapy was described initially in 1970 by McMillan et al. [15]. The idea was to maintain stable FVIII levels without the deep troughs that regularly accompany BI and expose the patient to the risk of bleeding (Fig. 2.1). However, it did not receive much attention because of technical issues related to the volumes required for infusion and concerns about the stability FVIII at room temperature and the potential for sepsis. Later it was observed that most FVIII concentrates are stable after reconstitution at room temperature for several days or even weeks [16, 17] and can be infused in small volumes of concentrated solution (with the addition of heparin to prevent local thrombophlebitis) via minipumps [18–20] to make CI a more accessible therapy.

Martinowitz et al. described the most accepted method in hemophilia centers [18]. This method employs pharmacokinetic dosing and takes advantage of decreasing clearance of coagulation

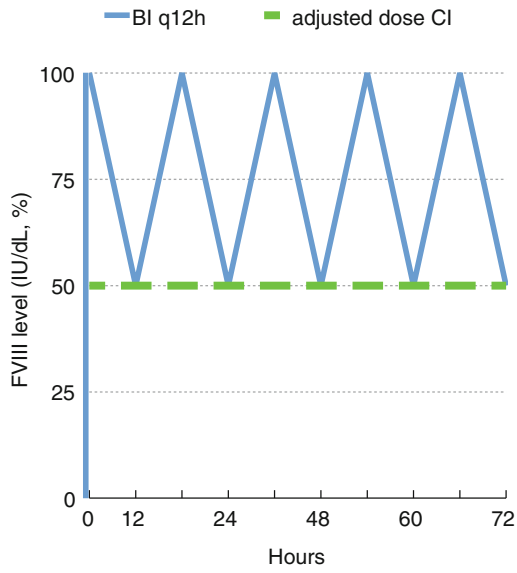

Fig. 2.1 FVIII levels in bolus infusion (BI) and adjusted continuous infusion (CI)

factor during CI. The simple protocol for this method is based on the following principles [18]:

1. Pharmacokinetic evaluation prior to a planned CI is recommended. The most important pharmacokinetic parameter for calculating the ideal rate of continuous infusion is the clearance. In the absence of preoperative pharmacokinetic evaluation or, in particular, in emergency situations, the initial maintenance dose may be calculated using the mean of a hemophilia population-based clearance, which is approximately 3.5 mL/kg/h for FVIII and 4.5 mL/kg/h for FIX.
2. The loading dose is calculated using in vivo recovery (IU/dL per IU/kg). A dose is selected that will raise the level to the desired minimum level appropriate for the surgical procedure requiring hemostatic replacement therapy, as mentioned before between 80 and 100 %.
3. CI is initiated immediately following bolus administration of the loading dose. The initial rate is calculated using the clearance obtained in the preprocedure pharmacokinetic evaluation according to the following steady-state equation:

   Rate of infusion (IU kg h) = clearance (mL kg h) × desired level (IU mL)

4. From the second day, the CI maintenance dose is adjusted using the same equation according to actual clearance, which is calculated from the daily factor level measurements.
5. Perioperative hemostatic demands may increase factor consumption beyond that expected. In order to prevent an undesired drop in the factor level, it is advisable to check factor activity 8–12 h after the start of CI and to increase the rate if necessary.
6. In most patients who require treatment for more than 1 week, a significant decrease in FVIII clearance is observed during the first 5–6 days of CI, followed by a plateau at a significantly lower level than that observed in the first days postoperatively [14, 18, 21]. This allows one to reduce the maintenance dose progressively and results in a significant sparing of concentrate.

CI is a safe mode of treatment, more cost effective, and should be the treatment of choice for major surgery in hemophilia patients [18]. Batorova and Martinowitz reported a reduction in the bleeding rates and FVIII dosage (36 %) compared with the use of BI [14].

2.3 Orthopedic Surgery in Hemophilia Patients with Inhibitors

The development of antibodies that inhibit or neutralize replacement therapy with factor (F) VIII or FIX is the most serious complication of hemophilia treatment today. Inhibitors develop in 20–30 % of patients with severe hemophilia A but in only 5 % of those with hemophilia B [22, 23]. Agents that "bypass" the need for FVIII or FIX are the mainstay of therapy for acute bleeds in inhibitor patients; however, the effect of such treatment is not as predictable as that of replacement therapy, and so it is more difficult to achieve bleeding control in hemophiliacs with inhibitors than in their non-inhibitor counterparts [24]. Therefore, inhibitor patients often have more severe joint morbidity than those without inhibitors, and older patients experience significant orthopedic disabilities [25, 26].

It should also be noted that another concern relating to the lack of treatment predictability in the inhibitor population is the need to monitor the effectiveness of bypassing agents using specific assays.

Until recently, orthopedic surgery in patients with inhibitors was strongly contraindicated; however, recent advances in our knowledge of effective hemostatic agents have improved our ability to adequately control surgical bleeding [27, 28]. Furthermore, contemporary advances in the orthopedic and hematological arenas have made it possible to successfully perform major orthopedic operations on hemophilic patients who have developed inhibitors [29]. Nevertheless, bleeding is still the most frequent and most serious problem encountered during orthopedic surgery.

The clinical conditions that define the indications for orthopedic surgery are the same for inhibitor and non-inhibitor patients – namely, chronic pain and severe disability, both of which produce stress and social isolation. However, as inhibitor patients face higher surgery-associated risks, they must be suffering from severe disability or intense pain before surgery can be considered and undertaken. It is extremely important that appropriate information is provided and that signed informed consent is obtained [30]. It is important to note, however, that despite the significant risk of bleeding, the results of orthopedic surgery in inhibitor patients are generally good but with a higher rate of complications than patients without inhibitors [28, 29].

It is important to follow international or consensus recommendations for hemostatic cover when performing orthopedic procedures in hemophilic patients with inhibitors [31–33] (Tables 2.3 and 2.4). Bypassing agents, recombinant factor VII activated (rFVIIa) and FEIBA (Factor Eight Inhibitor Bypassing Agent), have been used according to empirical dosing guidelines, without any laboratory monitoring. However, these agents are potentially thrombotic, and their effect is not as predictable as that of replacement therapy. Several laboratory assays have been proposed as potentially useful in monitoring bypassing therapy, including thrombography, thromboelastography (TEG) and rotational thromboelastography (roTEG), assessment of platelet contractile force, the Clot Signature Analyzer®, the modified ACT test, and the thrombin generation test [11]. The most important limitation of all these methods is that no assay end point to date has been demonstrated to correlate with clinical outcome, and these tests are not yet validated.

Replacement therapy should commence before surgery and continue during postoperative rehabilitation, but when should it be stopped? Surgical support should continue for 14 days after surgery [34]; because rehabilitation can trigger a bleed, so we recommend using a reduced cover dose just before the intense rehabilitation sessions for several weeks (one dose before each

Table 2.3 Recommended dosage of FEIBA® (Factor VIII Inhibitor Bypassing Agent) for surgery [34]

FEIBA®	Preoperative (U/kg)	Day 1–day 5	Day 6–day 14
Minor procedure	50–75	50–75 U/kg q12–24 h 1–2 doses	
Intermediate procedure	75–100	75–100 U/kg q8–12 h	75–100 U/kg q12h
Major procedure	75–100	75–100 U/kg q8–12 h	75–100 U/kg q12h

Table 2.4 Recommended dosage of rFVIIa (recombinant FVII activated) for surgery [34]

rFVIIa	Preoperative	Day 1–day 5	Day 6–day 14
Minor procedure	90–120 μgr/kg (ped. 120–150 μgr/kg)	90–120 μgr/kg q2 up to 4 doses q3–6 h for 24 h	
Intermediate procedure	120 μgr/kg (Ped. 150 μgr/kg) q2h	90–120 μgr/kg q2 day 1 Q3h day 2 Q4h day 3–5	90–120 μgr/kg q6 h
Major procedure	As above	As above	As above

rehabilitation procedure). This is an expensive treatment regimen, but development of a wound hematoma might jeopardize the long-term outcome and thus incur even more expense [35].

Conclusions

Hemophilia A and B are X-linked recessive bleeding disorders caused by deficiency of factor VIII (FVIII) or factor IX (FIX), respectively. Depending on the concentration of FVIII or FIX coagulant activity in blood, the disorders may be classified as severe (<1 % of normal activity), moderate (1–4 %), or mild (5–25 %). The hallmarks of clinical symptoms of hemophilia are joint and muscle bleedings, bruising, and prolonged severe hemorrhage after surgery or trauma. Surgery in patients with hemophilia carries a high risk of bleeding and represents one of the most challenging areas in hemophilia care. Most surgical and invasive procedures can be carried out safely in patients with hemophilia with factor replacement therapy. A favorable outcome depends on coordination between multidisciplinary team members. It is also crucial to ensure that orthopedic procedures in hemophilia patients are performed in specialized centers by an experienced team.

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Hemophilic Hemarthroses: Diagnosis and Management

3

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3.1 Introduction

The most typical manifestation of hemophilia is articular bleeding (hemarthrosis). Hemarthrosis is the major cause of disability and reduced quality of life in patients with factor VIII (hemophilia A) or factor IX (hemophilia B) deficiency [1]. When hemarthroses become frequent and/or intense, the synovium may not be able to reabsorb the blood. To compensate for such reabsorptive deficiency, the synovium will hypertrophy, resulting in what is called chronic hemophilic synovitis [2–7]. Thus, it is very important not only to avoid acute hemarthrosis but also to manage it as efficiently as possible, with the aim of avoiding the development of synovitis.

Hematological prophylactic treatment from the age of two to the end of skeletal maturity is the best way to avoid articular bleeds or at least to diminish their intensity. Prophylaxis with recombinant factor VIII or IX can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia [8, 9]. However, one should remember that problems may be caused by the permanent intravenous infusion needed in such circumstances. Two bypassing agents, a plasma-derived activated prothrombin complex concentrate [aPCC (FEIBA; Baxter AG, Vienna, Austria)] and NovoSeven [recombinant factor VIIa (rFVIIa); NovoNordisk, Denmark] are available for prophylaxis in patients with hemophilia who have developed inhibitors. Results from recent retrospective studies demonstrate the efficacy and safety of both aPCC and rFVIIa in decreasing the frequency of bleeding episodes in patients with hemophilia and inhibitors [10].

The early management of intra-articular bleeding has the potential to prevent chronic joint disease [11]. Most hemophilia centers in developed countries have on-demand treatment, which consists of the administration of the deficient coagulation factor when hemarthrosis occurs. It is important to differentiate acute bleeding and subacute bleeding. Subacute hemarthrosis is generally associated with previous synovitis or arthropathy, while acute hemarthrosis commonly occurs in a previously healthy joint.

3.2 Acute Hemarthroses

Acute bleeding can be felt by the patient as a burning sensation in the joint. Hemarthrosis develops within a few hours; the joint becomes

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_3,

Table 3.1 Different modalities used in the treatment of acute hemophilic hemarthroses

Hematological treatment
Rest and splinting
Ice
Analgesia
Arthrocentesis (joint aspiration)
Arterial embolization

inflamed, tense, and warm, and the skin becomes bright red. The affected joint is held in an antalgic flexion position, with painful and limited mobility. Table 3.1 shows the different existing modalities for the treatment of acute hemophilic hemarthroses.

3.2.1 Hematological Treatment

On-demand therapy with a plasma-derived or recombinant FVIII or FIX concentrate is the first-line treatment for acute bleeding episodes in patients with hemophilia [1, 9]. Dosing ranges from approximately 20 to 40 IU/kg administered until bleeding stops. That means the infusion of FVIII 40 IU/kg at the time of joint hemorrhage and 20 IU/kg at 24 and 72 h after the first dose. Patients must be then encouraged to continue infusions of 20 IU/kg every other day, until joint pain and impairment of mobility had completely resolved.

Ultrasonography (USG) is very important in acute hemarthroses as it can be used to objectively identify the presence of blood in the joints, measure its size, assess its evolution, and confirm its complete disappearance [12].

In patients with inhibitors, rapid control of bleeding episodes using bypassing agents has the potential to minimize joint damage and to improve quality of life [13]. Smejkal et al. evaluated the efficacy and consumption of FEIBA in treatment of hemorrhages in hemophiliacs with factor VIII inhibitor [14]. The median cumulative dose of FEIBA per bleeding episode was 205 U kg (−1). Bleeding was stopped in 97 % of events, but re-bleeding occurred in 5 % of events within 48 h after cessation of bleeding.

A study indicated that frequently bleeding inhibitor patients are prescribed and use higher rFVIIa dosing for all bleed types than recommended in the package insert (90 mcg kg(−1)) [15]. The rFVIIa dosing was highly variable, particularly in the first days of treatment.

A global, prospective, randomized, double-blinded, active-controlled, dose-escalation trial evaluated and compared one to three doses of vatreptacog alfa at 5, 10, 20, 40, and 80 lg kg(−1) with one to three doses of rFVIIa at 90 lg kg(−1) in the treatment of acute joint bleeds in hemophilia patients with inhibitors [16]. A high efficacy rate of vatreptacog alfa in controlling acute joint bleeds was observed; 98 % of bleeds were controlled within 9 h of the initial dose in a combined evaluation of 20–80 lg kg(−1) vatreptacog alfa.

After administration of the appropriate doses of factor concentrates, pain will rapidly diminish, although inflammation and limitation of articular mobility commonly disappear more slowly. The degree of inflammation and limitation of motion are always related to the amount of blood in the joint.

3.2.2 Rest and Splinting

Rest for lower limb bleeding episodes should include bed rest (1 day) followed by avoidance of weight bearing and the use of crutches when ambulating and elevation when sitting (3–4 days).

For the knee a compressive bandage is adequate, although in very painful cases the bandage should be supplemented with a long-leg posterior plaster splint. For the ankle, a short-leg posterior plaster splint is recommended. For the upper limb, usually a sling (for the shoulder) or a long-arm posterior plaster splint (for the elbow) will provide sufficient rest, support, and protection. Lifting and carrying heavy items should be avoided until the bleeding has resolved (4–5 days).

3.2.3 Ice

Ice therapy could help to relieve pain and reduce the extent of bleeding, although its current role in hemophilia remains controversial. Experimental

cooling of blood and/or tissue can significantly impair coagulation and prolong bleeding. In persons with hemophilia with acute hemarthrosis, ice application could impair coagulation and hemostasis [17].

3.2.4 Analgesia

For pain, paracetamol should be administered. Usually the hematological treatment provides adequate relief. Aspirin-containing products must be avoided. Unfortunately, there are no detailed algorithms or guidelines for pain management in hemophilia patients [18].

3.2.5 Joint Aspiration (Arthrocentesis)

Joint aspiration is not commonly performed, but in cases of severe bleeding, it may relieve the patient's pain and speed up rehabilitation (Fig. 3.1). There is a great deal of controversy on the role of arthrocentesis in hemophilia.

Arthrocentesis should be performed in major hemarthrosis (very tense and painful joints) [19]. Joint aspiration should always be done under factor coverage and in aseptic conditions, in order to avoid recurrence or septic arthritis. When hemarthrosis does not respond to hematological treatment, septic arthritis must be suspected, especially if the patient is immunodepressed; joint aspiration and culture will allow us to reach a diagnosis [20].

If hemarthrosis does not respond to hematological treatment, one must suspect hemophilic synovitis, which can be detected by clinical examination. USG and magnetic resonance imaging (MRI) will help confirm the occurrence of synovitis. In such cases only aggressive treatment of synovitis will allow us to control articular bleeding, which is secondary to synovial hypertrophy. Synovitis can be controlled with early prophylactic treatment or by synovectomy (radiosynovectomy or arthroscopic synovectomy). Diagnostic imaging is paramount to assess the response to any type treatment.

Heim et al. [21] reported an interesting case of a person with hemophilia who had a fixed flexed hip and intractable pain. This clinical picture was suggestive of hemorrhage in that area. USG confirmed the diagnosis of acute hip hemarthrosis. Narcotic drugs failed to alleviate the severe pain. Joint aspiration produced dramatic pain relief and early joint rehabilitation. However, Heim et al. did not suggest that every coxhemarthrosis

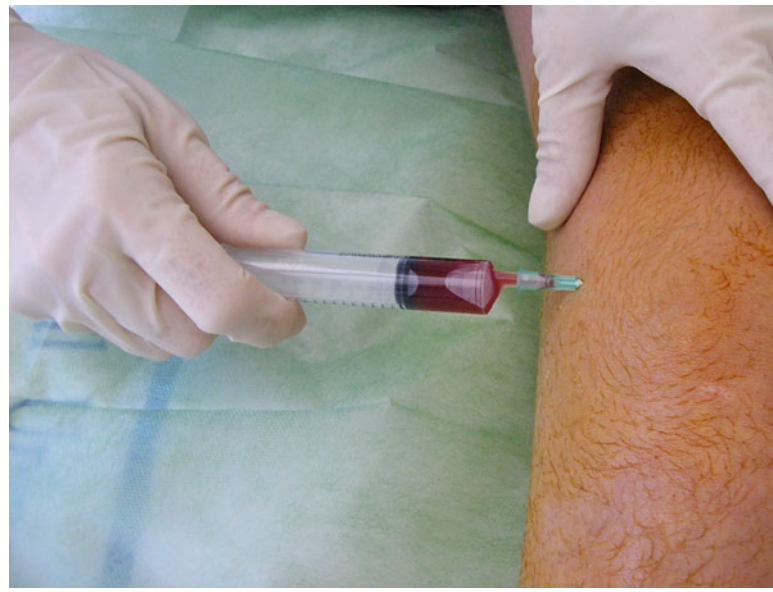

Fig. 3.1 Arthrocentesis (joint aspiration) in acute hemarthrosis of the knee in a hemophiliac. This must be done to relieve the pain and avoid the risk of future joint damage, although always with suitable hemostatic cover

should be aspirated. It should be remembered that raised intra-articular pressure may contribute to femoral head necrosis in adults or to Perthes' disease in children.

It is important to emphasize that while arthrocentesis of the elbow, knee, and ankle are quite simple procedures that can be done at the outpatient clinic, both shoulder and hip joint aspirations require sedation and radiographic control by an image intensifier, that is to say, they are surgical procedures done in an operating room, with an anesthetic and by an orthopedic surgeon.

3.2.6 Arterial Embolization

Klamroth et al. [22] reported seven patients who experienced recurrent massive bleeds that required arterial embolization. Under low-dose prophylactic treatment (15 IU fVIII or fIX per kg bodyweight for three times per week), no recurrent severe bleed unresponsive to coagulation factor replacement occurred after a mean observation time of 16 months after embolization. The consumption of factor concentrate decreased to one-third of the amount consumed before embolization.

In 21 cases of massive joint bleeding in 18 patients with hemophilia, selective catheterization was performed, and the bleeding was completely controlled by a single procedure in 14 cases [23]. Recurrence of the bleeding occurred in 7 cases and required a second embolization procedure; in one patient even a third embolization was required to stop the bleeding completely.

Selective angiographic embolization of the knee and elbow arteries was successful in 29–30 procedures [24]. Three patients remained free of bleeding events for more than 6 months. Additionally, after the procedure there was a significant reduction in factor FVIII usage that sustained up to 12 months after the procedures. No serious adverse events were observed. Therefore, angiographic embolization might be considered as a promising therapeutic and coagulation factor saving option in joint bleeds not responding to replacement of coagulation factor to normal levels [25].

Diagnosis and treatment of intra-articular hemorrhages must be delivered as early as possible. Additionally, treatment should ideally be administered intensively (enhanced on-demand treatment) until the resolution of symptoms. Joint aspiration plays an important role in acute and profuse hemarthroses. USG is an appropriate diagnostic technique to assess the evolution of acute hemarthrosis in hemophilia [26].

3.3 Recurrent Hemarthroses

Recurrent hemarthroses commonly occur after two or three articular bleeding episodes and persist despite adequate hematological treatment. Pain can be tolerable and is commonly associated with hypertrophic synovium on palpation and a slight lack of joint mobility.

When subacute hemarthroses recur for months and years, they will result in a state of hemophilic arthropathy. This usually occurs in young adults, who complain of persistent pain in the affected joint, not only with movement but also at rest. They may also have intermittent episodes of acute pain and inflammation related to synovitis or articular bleeding.

It is advisable to treat recurrent hemarthroses with hematological substitutive therapy, with two to three weeks of immobilization by means of a semiflexible splint. Some studies recommend 6–8 weeks of prophylaxis with physiotherapy. It is recommended to administer enough of deficient factor, three times a week, to obtain 20–30 % of the normal level. After each transfusion the patient should complete an exercise program focusing on active joint mobility, under the surveillance of an expert physiotherapist. If such mobility exercises are painful, only isometric exercises should be done.

When a flexion contracture does appear, it should be treated early and aggressively by conservative means to avoid it from becoming irreversible. Conservative measures include inverted dynamic splints, hinged extension–desubluxation casts, dynamic splints, and traction followed by a polypropylene orthosis. Inverted dynamic splints were specially designed for the knee joint and

require admitting the patient to hospital. The lower limb is put in a balanced traction on a semicircular Thomas splint which has a knee flexion Pearson's device. Then soft traction is put on the calf with the heel free; a posterior force is applied on the thigh by means of a cushioned spring located on the distal part of the thigh, which is connected by means of a string to a 3 kg weight. Such a posterior force counteracts the anterior force produced by the springs located on the posterior part of the calf. Both the longitudinal traction and the thigh weight are progressively increased. When the knee becomes fully extended, or if the technique does not work after one week of treatment, the patient is mobilized with a Böhler cast which is open in its anterior part.

The hinged extension–desubluxation cast can be made of plaster of Paris or of a thermoplastic material; it should be open in its anterior part. The hinge is adjusted once or twice a day to correct the deformity. When the contracture is less than 20°, the cast can be removed and replaced with a plaster splint. Hematological substitutive therapy is necessary during the procedure. The dynamic splint is adjustable and allows a low intensity but long duration force through the knee joint. A gain of 5–10° of knee extension can be expected in 6–9 months with this procedure. However, many patients may have hemarthrosis during the follow-up. Traction followed by orthosis is another alternative.

Flexion contracture has a different treatment and prognosis, depending on its chronicity and other associated deformities. A flexion contracture of few days' duration can be corrected by means of a traction followed by rehabilitation and orthosis. A flexion contracture with a duration ranging from weeks to months may require surgery: hamstrings release and/or supracondylar extension osteotomy. A flexion contracture associated with osseous or fibrous ankylosis may also require a patellofemoral osteotomy.

Radiosynovectomy (RS) is easy to perform and not a very expensive procedure (e.g., $4,500 US per injection). Moreover, it is very efficient in diminishing the frequency and intensity of recurrent hemarthroses related to chronic hypertrophic hemophilic synovitis. It should be performed as soon as possible in order to try to halt the long-term damage that intra-articular blood will produce in the involved joint. Personal experience and the general recommendation among orthopedic surgeons and hematologists is that when three early consecutive RSs (repeated every 6 months) fail to halt synovitis, and a surgical synovectomy (open or by arthroscopy) should be immediately considered.

The main radioactive materials used by the author have been 90-yttrium (90-Y) for the knees and 186-rhenium (186-Rh) for the elbows and ankles. RS is the "gold standard" of today for the treatment of chronic hemophilic synovitis once hematological treatment fails. Considering the current situation of radioactive materials in the world and their high cost and risk of being out of date, the practical point of view is that it is necessary to organize groups of patients (e.g., six to eight) to be injected. This means that sometimes the first patients of each group could wait up to 3–6 months until the group is complete. In such cases, patients should be in prophylactic hematological management while waiting. Good coordination among the members of the hemophilia center, those of the department of radioactive isotopes, and the enterprises that produce the radioactive material is paramount.

RS has a mid- and long-term efficacy of 70 % [27–33]. From the clinical point of view, such an efficacy is demonstrated by the decrease (or even disappearance) in the number of hemarthroses. In general terms, it can be said that RS has a fibrosing effect on the synovium, transforming a bleeding and richly vascularized synovium into a sclerotic and poorly vascularized tissue. It should be emphasized that in 30 % of cases, the first RS is not efficient enough and hence should be repeated.

Up to three RSs are recommended, with a 6-month interval between them [28]. When repetitive RSs fail, a surgical synovectomy would be indicated. There is a controversy concerning the use of surgical open synovectomy versus arthroscopic synovectomy. The author prefers an arthroscopic synovectomy ($60,000 US per procedure), provided that an adequate substitutive

hematological treatment is made and an appropriate postoperative rehabilitation is established.

The review of the literature and the author's 38-year experience have demonstrated that the safety of an RS is maximum [27–33]. The most serious potential problem in RS is skin burns because of extravasation of the radioactive material out of the joint at the time of injection. Another potential complication is an intense inflammatory reaction that may occur after the procedure. In such cases, rest and nonsteroidal anti-inflammatory drugs commonly solve the problem. In one case, a bilateral ankle 90-Y RS eventually caused a bilateral fixed equinus deformity that required a bilateral Achilles tendon lengthening to solve the problem. The potential malignant effects of RS have not been published after more than 40 years of using such materials all over the world.

Although highly cost-effective in comparison with surgical or arthroscopic synovectomy, the risk of cancer associated with RS is not well known. Infante-Rivard et al. evaluated the incidence of cancer in a group of patients treated with RS, and no increase in the risk of cancer was observed [34]. There was no dose–response relationship with the amount of radioisotope administered or number of RS treatments. The study provided some indication for the safety of the procedure, but homogenous diagnostic groups of younger patients (such as hemophilic patients) receiving RS will need more evaluation. The alternative to RS is arthroscopic synovectomy which can effectively control the hypertrophic synovium and resultant bleeding and can be used safely even in very young patients [34]. Our current indication of RS is in children older than 12 years of age.

Conclusions

Optimal treatment of acute hemarthroses involves a combination of factor replacement, joint aspiration, rest (with or without splinting), ice, appropriate analgesia, and supervised rehabilitation once the acute phase has been controlled and the risk of bleeding reduced. The objectives of treatment are to avoid muscular atrophy, maintain an adequate degree of articular mobility, control the recurrence of hemarthroses, and recover joint function if possible. The main indication for a radiosynovectomy (RS) is the existence of chronic hemophilic synovitis, which causes recurrent hemarthroses unresponsive to hematological treatment. The rate of efficacy of RS ranges between 75 and 80 %. RS can be repeated if the first one fails; it may be performed up to three times at 6-month intervals. After 40 years of using RS all over the world, no damage related to the radioactive isotopes has been found. RS with 90-Y or 186-Rh is the optimal procedure to follow, provided it is available. RS is a relatively simple, virtually painless, and inexpensive technique for the treatment of chronic hemophilic synovitis, even in patients with inhibitors. Thus, RS is the best choice for patients with persistent synovitis.

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Imaging of the Hemophilic Joints

4

Carmen Martín-Hervás

4.1 Introduction

Joint disease affects 90 % of people with severe hemophilia and contributes the greatest morbidity and cost in the hemophilia population. Recurrent joint bleeds result in progressive arthropathy. The ankles, knees, and elbows are the joints most frequently involved [1]. It is important to diagnose and monitor joint changes in order to make therapeutic decisions. The radiographic findings of hemophilic arthropathy (HA) depend on the stage of disease, the age of the patient at onset, and the joint involved. These findings include joint effusion, soft tissue swelling, epiphyseal overgrowth, subchondral cysts, osseous erosion, and secondary degenerative changes [2]. The imaging techniques, conventional radiography (x-ray), ultrasonography (US), and magnetic resonance imaging (MRI), may become useful for the evaluating HA [3].

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4.2 Radiography

X-ray has been successfully used for decades to objectively evaluate and stage HA [4]. Findings of HA demonstrated on x-ray include osteoporosis, osteonecrosis, epiphyseal overgrowth, widening of the epichondral notch of the knee, bone cysts, joint space irregularity and narrowing, angulations of the knee and ankle, and bony fusion [1]. Plain films underestimate the degree of joint pathology. However, although radiography visualizes primarily bone lesions, it is insensitive to the early changes of HA and to the less advanced joint damage seen in patients receiving prophylactic treatment [5]. The earliest changes in HA are to the synovium, and these soft tissue changes are poorly demonstrated on x-ray [4]. Osseous changes due to hemorrhage only appear late in the disease. Cartilage destruction cannot be visualized directly, but only inferred from changes, such as loss of joint space and an irregular subchondral surface. Assessment of joint space loss is difficult in children, particularly if comparison films are not available [6]. There are two main classification systems in use for grading HA on x-ray. These are the Arnold-Hilgartner scale, described in 1977 [7] and the Pettersson score described in 1980 [4]. The Arnold-Hilgartner system is a progressive scale for the assessment of HA, the worst imaging finding

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_4, © Springer International Publishing Switzerland 2015

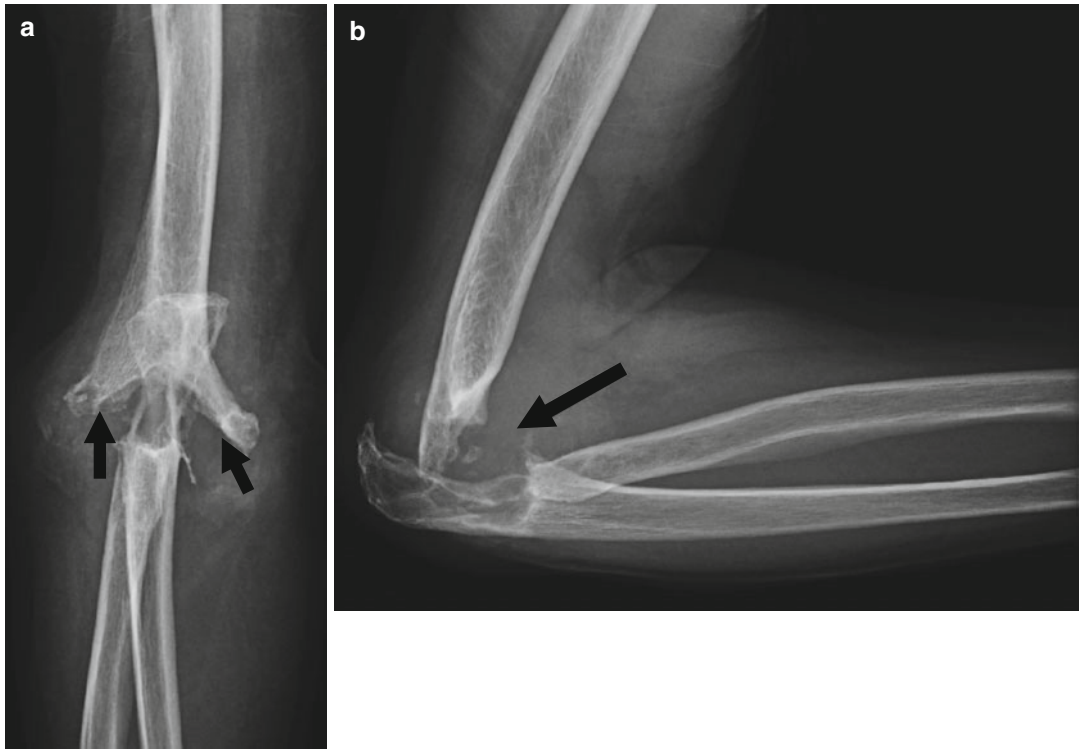

Fig. 4.1 Anteroposterior (**a**) and lateral (**b**) lateral radiograph has to be turned 90º to the right, on the same way as a watch (*arrows*)

reflecting the stage of the arthropathy [7]. The Pettersson score is an additive scale [4]. Each abnormality is graded from 0 to 1 or 2, and abnormalities due to different stages of the disease will all be included. The highest score for an individual joint is 13, which indicates a totally destroyed joint [4] (Fig. 4.1). There are differences between the two scoring systems. The progressive one is simple and easy to use by everyone. The additive one is more meticulous, but discriminates better between different stages of HA.

One study assessing both intra- and interobserver variability of the two scoring systems demonstrated generally good correlation if there is minimal or maximal joint disease, but poor levels of agreement if there is mild or moderate HA [8]. The World Federation of Hemophilia recommends the Pettersson score for universal use [9].

Once radiographic changes are present, the clinical course of the arthropathy is usually progressive and irreversible. Improved therapy has led to the need for more sensitive tools for the assessment of the degree of joint damage, which can evaluate the subtle joint changes not seen on plain film. However, once the disease is advanced, it can usually be monitored with x-ray alone [5]. Soft tissue swelling can be suggested, but is often not clearly delineated (Fig. 4.2).

4.3 Ultrasonography

US is an imaging technique with a progressive and extensive use in the musculoskeletal system and can be a useful complementary technique in the evaluation of HA, which is readily available and does not require the child to be sedated. US

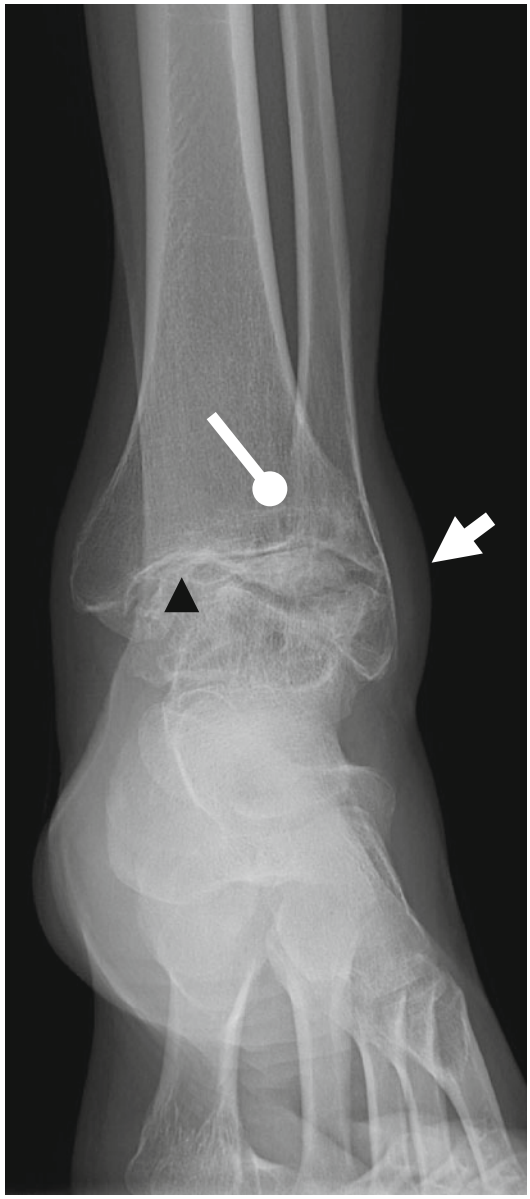

Fig. 4.2 X-ray anteroposterior (AP) view of the ankle demonstrating soft tissue swelling (*arrow*), osteoporosis, epiphyseal overgrowth, subchondral bone cyst (*round arrow*) with significantly narrowed joint space (*arrowhead*)

has some other potential advantages, including lack of ionizing radiation, cost- and time-effectiveness, accessibility, and real-time and dynamic examinations. In this way, US can be used as a first diagnostic imaging procedure instead of MRI. The major disadvantage of US is its operator dependence, requiring a long learning curve and a limited value of images for orthopedic surgeons and physicians that prefer a more anatomical imaging modality, such as MRI [10].

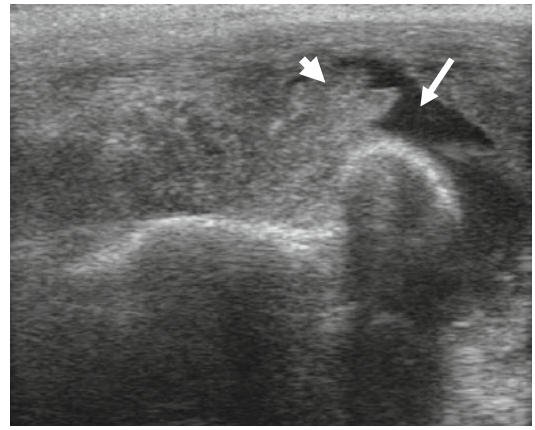

Fig. 4.3 Elbow. US longitudinal view of the radial head with joint effusions (*arrow*) and severe synovial thickening (*arrowhead*) demonstrated as a hypoechoic tissue

Linear high-resolution (7–17 MHz) probes are typically used for assessing HA [11], enabling the visualization of superficial musculoskeletal structures such as synovium, tendons, musculature, and the cartilage/osteochondral interface at the edge of the joints on grayscale sonograms. US can also be used to follow the progression or regression of soft tissue hematomas and pseudotumors [2].

US can be used to assess joint effusions in acute episodes. US as a diagnostic technique in the initial stages of hemophilia permits the differentiation between effusion and synovial thickening (Fig. 4.3). A selective compression with the US probe may help to distinguish both entities; the fluid will be displaced out, while the synovium remains incompressible [10, 12]. A hemarthrosis may demonstrate a different echogenicity, depending on the stage of degradation of the blood products [11]. The normal synovium is a thin membrane. When it becomes inflamed, diffuse or nodular thickening of the membrane is seen, which may show increased vascular flow on Doppler US. Differentiation between hemarthrosis and synovial hypertrophy helps to determine when factor replacement is necessary for patients

treated on demand [5]. The selective implementation of prophylaxis would require the availability of a more sensitive tool to monitor for the development of synovitis than is currently possible with clinical surveillance or x-ray. MRI is such a tool and is utilized for the evaluation of HA [13]. However, MRI is expensive and requires sedation in younger children, precluding its utility for monitoring synovitis [14].

US with power Doppler has been used to detect and quantify vascularity in other arthritides [15] and has the capability of evaluating synovial vascularity in hemophilic joints. A recent study [16] showed a strong correlation between Doppler and dynamic contrast-enhanced MRI measurements in hemophilic knees, elbows, and ankles.

In fact, contrast-enhanced US may be comparable to MRI in estimating synovial vascularity for the diagnosis of active synovitis as seen with rheumatoid arthritis [17]. US also reveals early cartilaginous involvement and partial visualization of the joints [17] (Fig. 4.4).

Previous studies evaluated the US findings of HA [11, 18] and described a systematic protocol for data acquisition of US findings in hemophilic joints [12, 19]. Nevertheless, the value of this technique for the assessment of HA in comparison with MRI and physical examination has not been fully evaluated so far. As a result, this technique has been underemployed in clinical practice. Another challenge of US relates to the interpretation of images and comparison with other diagnostic tests.

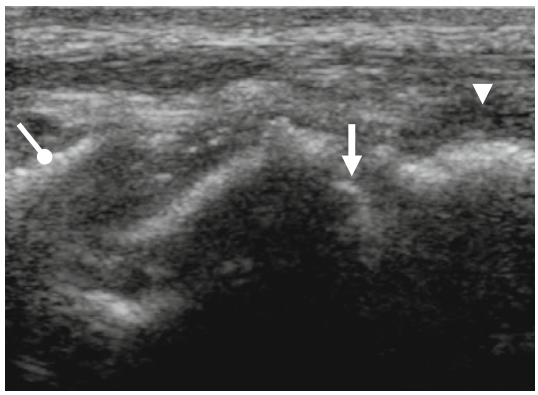

Fig. 4.4 Ankle. US longitudinal view over the anterior tibiotalar joint shows narrowing of the joint space, tibial bony spur (*round arrow*), mild synovial hyperplasia (*arrowhead*), and irregularity of the hyaline cartilage and subchondral plate of the talar dome (*arrow*)

4.4 Magnetic Resonance Imaging

MRI was introduced as a medical imaging modality in the 1980s, and it uses radio waves and magnetic fields [3].

MRI has been shown to more accurately assess a HA than radiography. MRI has obvious advantages, including the increased level of detail of soft tissue and cartilage changes and lack of ionizing radiation, but it is more costly, less accessible, and more time consuming and requires sedation in younger children [6, 14].

MRI provides information on all aspects of HA, demonstrating early arthropathic changes such as hemarthrosis, effusion, synovial hypertrophy, hemosiderin deposition, and small focal cartilage defects without joint space narrowing, which cannot be delineated by x-ray imaging. Moreover, MRI can provide information about more advanced changes, such as erosions, subchondral cysts, and cartilage destruction with joint space narrowing [5, 17] (Fig. 4.5).

There has been shown to be a high correlation between the presence of osseous changes on x-ray and the presence of synovial or cartilaginous changes on MRI, especially in the advanced stages of the disease. The sensitivity of MRI to detect the changes of early HA is high [20], but is lower for the elbow than for the knee or ankle [5].

Exact recommendations of the sequences to be performed in HA have not been established [6]. A T1-weighted sequence is always useful to demonstrate anatomy and osteochondral lesions. A short T1 inversion recovery (STIR) sequence is very sensitive for demonstrating bone edema (Fig. 4.6), and gradient-echo (GRE) sequences improve the visualization of the cartilage, synovium, and hemosiderin [17, 21]. T2* GRE sequence results in enhanced visibility of blood products in the acute stage (deoxyhemoglobin) and the chronic stage (hemosiderin) and can identify even the smallest amount of hemosiderin

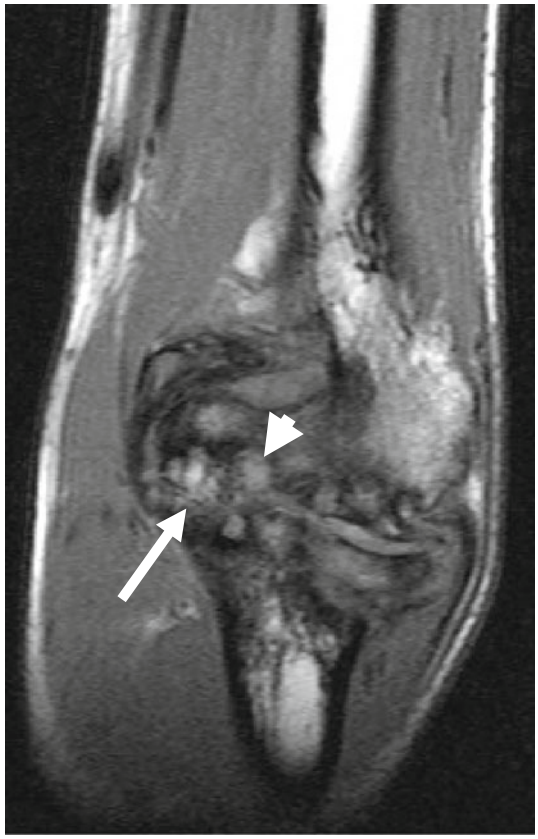

Fig. 4.5 The T1-weighted MRI coronal view of an elbow shows erosions, subchondral cysts (*arrowhead*), and cartilage destruction with joint space narrowing (*arrow*)

deposition in a joint [21] (Fig. 4.7). However, when there is a significant amount of hemosiderin in the joint, the degree of susceptibility artifact may be too great to enable interpretation.

Detailed images of cartilage can be obtained with either a proton density fat-saturated sequence or a fat-suppressed, three-dimensional, spoiled gradient-echo sequence [21].

Synovial hypertrophy is usually an intermediate signal on T1- and T2-weighted images, enabling differentiation from fluid within the joint. However, active synovitis may show signal characteristics similar to that of fluid [5]. Enhancement of the synovium with intravenous contrast media may theoretically help distinguish active synovitis from fibrotic synovium [6]. However, the presence of fibrosis and hemosiderin within the proliferative synovium in HA limits the degree of visible enhancement. Therefore, intravenous contrast medium is not routinely recommended in the evaluation of HA; it also increases the invasiveness and the cost of the examination [6, 20–23].

MR is a powerful tool in the diagnosis, staging, and treatment of patients with HA. To measure arthropathic changes in clinical practice and in clinical research trials, tentative hemophilic arthropathy scales based on MRI findings

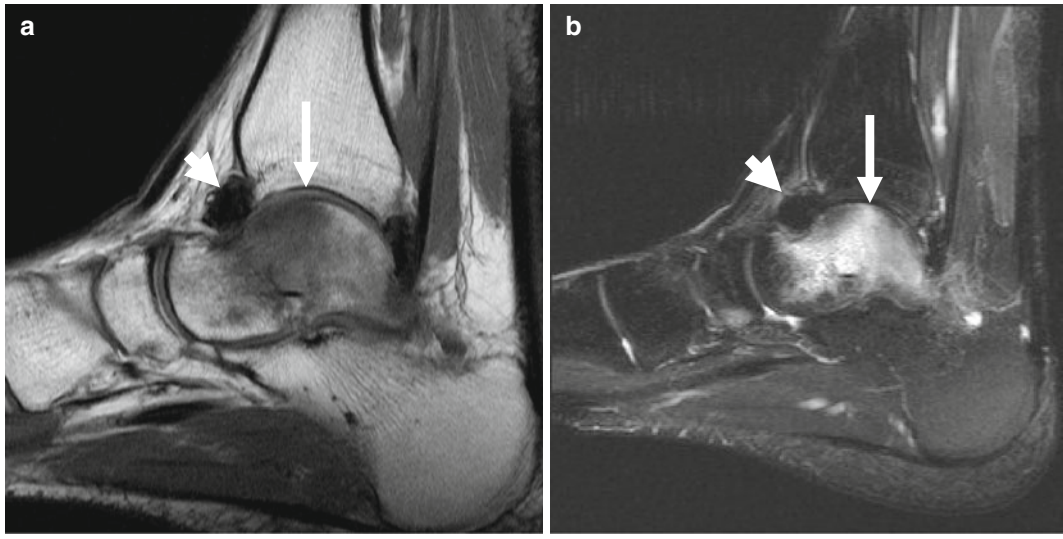

Fig. 4.6 Sagittal T1 (**a**) and STIR (**b**) images of the ankle, demonstrating bone edema of the talar dome (*arrow*) and synovial hypertrophy with iron deposit in the tibiotalar joint (*arrowhead*)

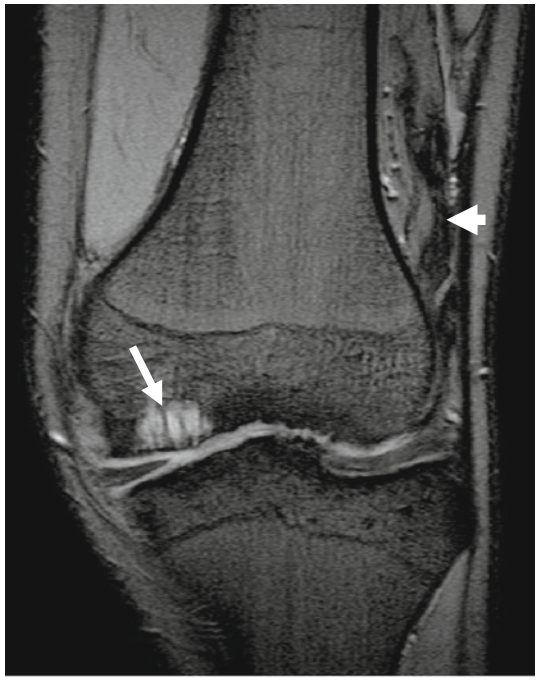

Fig. 4.7 The GRE T2* coronal MRI view of a knee shows subchondral cysts (*arrow*) and mild hemosiderin deposits (*arrowhead*) intensely black, conversely to the adjacent soft tissues

have been developed in the last decade [13, 20, 24, 25].

The first MRI staging system reported was the Denver scale from Nuss et al. in 2000 [13]. This is a progressive scoring system, modeled on the Arnold and Hilgartner scale, with the worst finding determining the score in a particular joint. However, as it measures only the depth of the cartilage, it is less discriminating between different degrees of cartilaginous change [5].

The European score is a more detailed additive score that was modeled on the Pettersson score [24]. This additive system is more complex than the Denver scale. However, it does allow the separate evaluation of osteochondral and soft tissue changes. It assesses both the depth and width of cartilage changes. Its greatest value is in the evaluation of moderate to severe joint changes, but it is also reported to be better than the Denver scale at discriminating between early and advanced arthropathy [25].

Several other MRI grading systems have also been suggested [20, 21, 23]. The development of many different MRI scoring systems threatens to hamper the comparison of results from different centers. In an attempt to standardize the MRI interpretation of HA, the International Prophylaxis Study Group developed the Compatible MRI Scale [25]. This scale combines a 10-step progressive component based on the Denver Scale and a 20-step additive component based on the European score, with identical definitions of mutual steps. The Compatible MRI scale is highly reproducible, is excellent in deciding the presence or absence of HA, but performs relatively poorly at discriminating mild disease from moderate and severe disease [5, 26].

4.5 Other Imaging Techniques

4.5.1 Computed Tomography (CT)

Both MRI and contrast-enhanced CT are useful in determining the thickness of the wall and the extent of hemophilic pseudotumors, more consistently than US [2]. They usually destroy adjacent bone [13].

4.5.2 Nuclear Medicine

Radiosynovectomy is effective in improving the function in hemophiliacs [27]. In spite of the potential value of scintigraphy for evaluating post-therapy joint changes, the limited spatial resolution of this imaging modality for the assessment of osteochondral abnormalities and its radiation-bearing potential has limited its use for follow-up of arthropathic changes, instead of US and MRI.

4.5.3 Positron Emission Tomography (PET)

PET is a technique that uses molecules labeled with isotopes that emit positrons from their

nucleus. The most commonly used tracer is 2-deoxy-2-(18 F) fluoro-*d*-deoxyglucose (FDG) [28]. After intravenous injection, FDG is taken up by the cells according to their level of glucose metabolism. Preliminary results demonstrated that the increased glucose metabolism of many inflammatory cell types and the FDG uptake by inflammatory tissues are the basis for the potential use of FDG-PET in the detection and monitoring of chronic HA in hemophilia [17].

Conclusions

Diagnostic imaging is used to objectively evaluate and stage hemophilic arthropathy. X-ray is useful to monitor advanced stages of the disease once considerable cartilage and/or bone damage has occurred in the joint. Ultrasonography can be used as a complementary technique to assess and follow up the soft tissue changes of the arthropathy. MRI, with its excellent soft tissue contrast, can accurately evaluate the early changes and the less advanced joint damage seen in patients receiving prophylactic therapy. MRI is the imaging method of choice for detecting the abnormalities of hemophilic arthropathy, staging their severity, and following the effects of treatment.

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Shoulder Surgery in Hemophilia

5

Elena Casado-Sanz, Raúl Barco-Laakso,
Samuel Antuña, and E. Carlos Rodríguez-Merchán

5.1 Introduction

Hemophilia is an X-linked recessive bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B). It can be severe (<1 % factor activity level), moderate (1–5 %), or mild (>5 %). The prevalence of hemophilic arthropathy correlates with the level of circulating clotting factor. Patients with severe hemophilia may have frequent spontaneous bleeding episodes.

There is little information available on the effect of hemophilia on the shoulder joint. Since the shoulder is not a weight-bearing joint nor is it a hinge joint, like the elbow, it is not as affected as the lower limb. The shoulder is the fourth most frequently affected joint after the knee, the ankle, and the elbow. Approximately 4 % of joint bleeding in patients with hemophilia has been reported to occur in the shoulder and occurs at a more advanced age than in other joints [1].

In the study by Chen et al., it was found that 50 % of the patients with hemophilia that were studied had hemarthrosis in the shoulder, and out of that 50 %, up to 39 % presented symptoms [1]. This correlates with MacDonald et al. in which there was a prevalence of 37 % of patients with symptoms [2].

5.2 Clinical Findings

In the shoulder, onset of hemarthrosis and chronic synovitis often occurs in adulthood as opposed to other joints that experience onset of hemarthrosis in childhood.

A single intra-articular hemorrhage may give rise to low-grade synovitis, which predisposes the target joint to recurrent hemarthrosis. A cycle of chronic synovitis, inflammatory arthritis, and progressive arthropathy is thus initiated.

Muscle atrophy and loss of motion occur early and in most patients. Acute hemarthrosis may present with inability to use the affected limb, prodromal stiffness, and warm sensation followed by acute pain and swelling. Progression to the subacute stage brings synovial hypertrophy and increased motion impairment. Repeated bleeds and degradation for more than 6 months constitute chronic hemarthrosis with severe limb impairment.

In older studies the prevalence of rotator cuff tears in hemophilia patients reached up to 20 % [2]. In more current research, up to 7.1 % of patients presented with full-thickness rotator cuff tears, 16.5 % of patients with partial thickness rotator cuff tears, and 60 % with bicipital tenosynovitis. Though these lesions increase with age in

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_5, © Springer International Publishing Switzerland 2015

patients without hemophilia, and in patients with hemophilia and bleeds, there is a higher incidence and the lesions are linked to greater joint damage as seen in x-ray [1].

In severe cases, impaired elbow motion makes loss of shoulder motion even more consequential. Progression to end-stage arthropathy takes many years, but is the usual course [3, 4].

5.3 Radiological Findings

The two radiographic grading systems for hemophilic arthropathy in general use are the Pettersson and the Arnold-Hilgartner classifications.

The Pettersson classification ranges from 0 to 13 and is based on radiographic evidence of osteoporosis, osteophytes, narrowing of the joint space, subchondral irregularity, subchondral cyst formation, erosion of the joint margins, and bone remodeling. A normal joint has a grade of 0. The Pettersson scoring system has been adopted by the world Federation of Hemophilia as the preferred radiographic classification system for hemophilic arthropathy.

The Arnold-Hilgartner system is based on five radiographic stages. The modified classification has four grades instead of five. This eliminates the original stage II (epiphyseal enlargement and juxta-articular osteoporosis) which is rarely a discrete stage and has no specific implications in treatment [4].

In a study by Cahlon et al., 822 patients were examined, of which 93 presented symptoms. Seventy-nine of the 83 showed abnormalities according to the Pettersson scoring system. In mild cases, the earliest symptoms are the formation of cysts in the greater tuberosity and light subchondral irregularities. As degeneration progresses, we can see glenoid osteophytes, subchondral and humeral head cysts, partial joint space narrowing, and marginal erosion (Fig. 5.1). In severe cases, there are severe marginal erosions, obliteration of the joint space, elevation of the humeral head, and humeral head and glenoid osteophytes (Fig. 5.2). In the final stages,

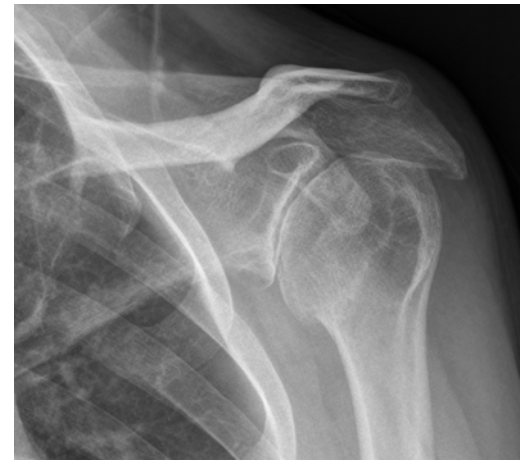

Fig. 5.1 Shoulder AP radiograph of a patient with pain and bleed episodes who has developed moderate degenerative changes with cysts in the humeral head and glenoid

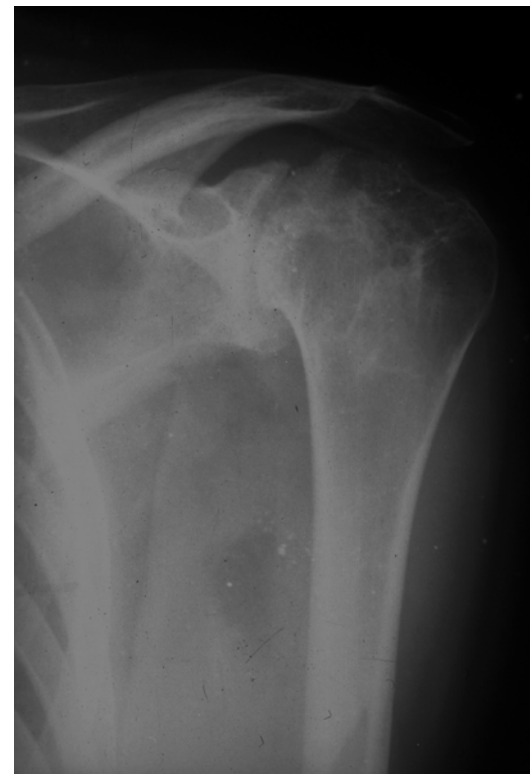

Fig. 5.2 Shoulder AP radiograph of a hemophilic patient with pain. There is significant elevation of the humeral head secondary to a massive chronic cuff tear and numerous cysts in the humeral head

a complete deformity of the glenohumeral joint can be observed [3].

In the same study, radiographic changes that correlated with the patient's clinic were observed. Only 32 % of patients with mild changes presented symptoms, while in those with moderate or severe changes, the percentage increased to 59 and 65 %, respectively.

The use of MRI in hemophilic arthropathy of the shoulder is very useful in the examination of soft tissues. With its use, the synovium bursa, tendon sheath, cartilage, and rotator cuff can be evaluated. Ultrasonography has proved a viable alternative on occasions in which an MRI cannot be conducted or is unavailable. Both methods have comparable precision in the identification of partial and total tears of the rotator cuff [5]. Ultrasonography is also a useful tool in identifying hemarthrosis and choosing the most appropriate treatment [1].

Patients with shoulder involvement most of the times require a TC before surgery to identify bone deficiencies, especially if a joint replacement is being considered. TC allows evaluation of the glenoid bone stock which would help in deciding if a total shoulder arthroplasty or a hemiarthroplasty is preferred [4].

5.4 Management

The key to the successful prevention of hemophilic arthropathy is management of initial hemarthrosis before the development of chronic synovitis and articular surface erosions.

As a result, prophylaxis studies have been developed. There is a distinction between primary and secondary prophylaxis. Primary prophylaxis would be used after the initial diagnosis or after the first bleeding episode, maintaining levels of clotting factor between 1 and 5 % via repeated injections [6]. However, this would be very expensive. The alternative treatment is secondary prophylaxis consisting of clotting factor injections after every bleeding episode until the complete recovery of acute hemarthrosis occurs [7].

5.4.1 Acute Hemarthrosis

In cases of acute hemarthrosis, the priority is to distinguish between patients with established arthropathy and those without. To that end, it is useful to use ultrasonography to discern the degree of hemorrhage and joint degeneration.

In patients with established arthropathy, the only reason to conduct an arthrocentesis would be to relieve pain and possibly improve mobility.

In cases in which there is no damage to the joint, arthrocentesis is recommended after factor replacement to avoid the buildup of proteolytic enzymes, immobilizing the joint for 2 weeks, followed by 2–4 weeks of physical therapy.

Steroid injection, combined with immobilization, is effective in some patients with chronic hemarthrosis [4].

5.4.2 Synovectomy

Synovectomy is recommended in cases of chronic synovitis in which no joint degeneration has occurred. While synovectomy prevents bleeds, thereby delaying joint degeneration, the procedure does not reverse changes that have already taken place in the joint.

There are documented gains from synovectomy. First, analgesia gained for excision the inflamed tissue. Secondly, the number of bleeding episodes can be reduced, and with this, the possible delay of the hemophilic arthropathy [8].

There are three methods for performing a synovectomy: medical (synoviorthesis), arthroscopic, and open.

Medical Synovectomy (Synoviorthesis)

This method acts as a chemical synovectomy and prevents synovial proliferation by introducing a fibrosing agent inside the joint that strangles the vessels.

Although many materials are available, radiocolloids have been the most widely used. Radiocolloids applied in synoviorthesis include

gold (Au 198 – no longer used due to gamma radiation), rhenium (Re 89), and yttrium (90 Y). The advantage of using these materials is that they require only one dose. The disadvantage is the high cost.

Rifampicin and oxytetracycline chlorhydrate are being examined as inexpensive alternative products. They both have similar fibrosing action and are used in a similar fashion in pleurodesis [9].

In the study by Fernández-Palazzi et al., 82 patients who had received repeated oxytetracycline chlorhydrate injections in the knees, elbows, and ankles were examined retrospectively. Significant improvements were observed in both range of mobility and pain [9].

Rezazadeh et al. studied the use of rifampicin injected into the knees, elbows, and ankles of 21 patients, and in the shoulder of one patient. A mean reduction of 6.3 bleeding episodes per month was obtained [10].

In conclusion, this method may reduce hemarthrosis, related pain, and also improve the range of motion in patients with hemophilic arthropathy. Chemical synoviorthesis appears to be efficient. The use of rifampicin and oxytetracycline chlorhydrate offers an inexpensive and simple alternative that may prove especially practical in developing countries where radioactive agents are not easily available. The disadvantage is that it may be necessary to repeat injections several times.

Arthroscopic Synovectomy

The primary indication for arthroscopic synovectomy is recurrent joint hemarthrosis with failure of appropriate medical management. Secondary indications include joint pain and loss of motion. The primary contraindication is advanced degenerative joint disease.

The benefits of this procedure as opposed to synoviorthesis include the ability to perform adequate synovial debridement, but also concomitant lysis of adhesion and capsular release to regain range of motion.

The disadvantages are higher risk of bleeding complications, requirement of anesthesia, and increased morbidity [11].

There have been no studies comparing the results of synoviorthesis to arthroscopic synovectomy and no studies which illustrate results of shoulder arthroscopic synovectomy in patients with hemophilia.

Open Synovectomy

It is less common in recent years to perform open synovectomy. It is known that it requires a large amount of antihemophilic factor (AHF), longer time in surgery, extended hospital time, and lengthy, difficult rehabilitation. After this procedure it is common to see some loss of previous range of motion.

5.4.3 Shoulder Replacement

There is limited information in the literature regarding shoulder arthroplasty for hemophiliacs. Concerns extrapolated from lower extremity arthroplasty in this population are significant. These include blood loss, wound healing, postoperative infection, HIV and hepatitis status of the patient, as well as concerns with long-term outcomes. In contrast with the shoulder experience, reconstructive surgery of the knee in hemophiliacs is well reported and has been largely successful [12].

In a study by Dalzell et al., two patients with hemophilia who underwent hemiarthroplasty were studied. The results in each case revealed a decrease in pain and an increase in ROM and function postoperatively. These findings suggest that hemiarthroplasty with postoperative physiotherapy may be a feasible option to manage severe, chronic, and progressing shoulder pain as a result of hemophilic arthropathy of the shoulder [13].

In a more recent study from 2011, seven shoulders were examined in six patients [12]. The average age of the patients was 47.6 years of age, and follow-up averaged 13.8 years. Total shoulder arthroplasty was performed on four shoulders, and in three cases hemiarthroplasty was chosen due to deficient bone stock in the glenoid site. In those three cases, a bone graft was done of the desiccated humeral head. Due to the prevalence of cysts, a TC

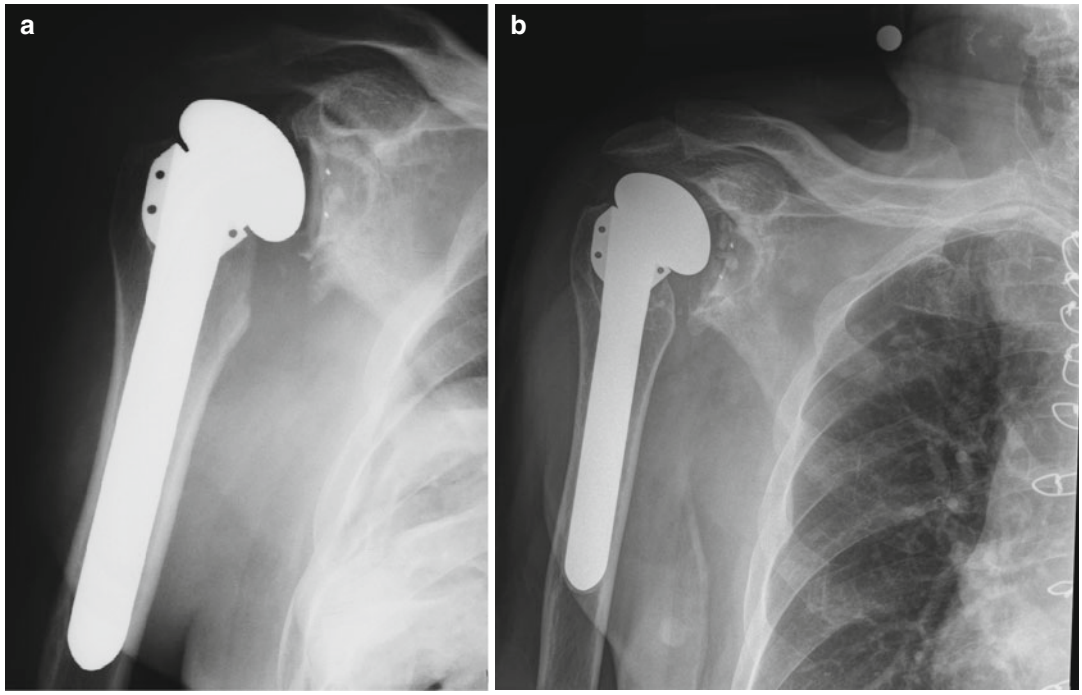

Fig. 5.3 Total shoulder arthroplasty in a patient with haemophilic arthropathy. (**a**) AP radiograph two years after surgery. (**b**) 5 years after surgery there is obvious loosening of the glenoid component with superior tilting (Courtesy of Dr. John W. Sperling)

is necessary for these patients in order to evaluate the bone stock at the glenoid site before surgery.

In five patients (six shoulders), there was a decrease in pain. The average for preoperative pain was 4.8, while postoperative pain was reduced to an average of 1.9. The average range of flexion increased from 106° to 131°, and external rotation increased from 20.7° to 40°. There was a decrease in average internal rotation, which went from L2 preoperative to L4 postoperative.

Based on the modified Neer score, there were two excellent, four satisfactory, and one unsatisfactory result. None of the shoulders required revision or reoperation.

Their results were better in total shoulder arthroplasty than in hemiarthroplasty, but the number of patients was too small to demonstrate a statistical difference. They concluded that total shoulder arthroplasty in hemophiliac patients may produce good results, but it is necessary to conduct in-depth preoperative analysis and confer with a hematologist to decrease the incidence of complications and obtain a favorable outcome [11, 12] (Fig. 5.3)

5.4.4 Arthrodesis

In recent years, arthrodesis has been almost abandoned in favor of shoulder prosthesis, though it offers the advantages of greater longevity, more strength in the extremity, and lower rates of infection. Arthrodesis must be performed on the joint with 20–30° of abduction, 30° of flexion, and 30–40° of internal rotation.

In classic studies the incidence of pseudarthrosis was elevated due to the use of the arthrodesis technique in only one plane. Currently, the complication rate of arthrodesis has decreased as it is performed in three planes by joining the glenohumeral, coracohumeral, and acromiohumeral joints [8]. There is, however, no experience of arthrodesis in the hemophilic shoulder and the majority of patients prefer an arthroplasty.

Conclusions

The shoulder is the fourth most common joint affected by recurrent hemarthroses in hemophilia. During the initial phases of the disease, synovectomy can reduce the joint damage and improve patient's symptoms. When the joint is severely damaged, shoulder replacement may be the only option for treatment. Replacement of the joint yields to satisfactory pain relief, especially when a glenoid component can be implanted. In cases with glenoid bone stock deficit, it may be impossible to replace it and hemiarthroplasty may be the only option.

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Surgery of the Elbow in Hemophilia

6

Raúl Barco-Laakso, Samuel Antuña, and E. Carlos Rodríguez-Merchán

6.1 Introduction

The elbow joint is the most affected joint in hemophilic arthropathy after the knees. The number of bleeding episodes is correlated with the degree of articular degeneration, so the actual standard of care is to reduce the number of bleeding episodes through prophylactic factor replacement therapy. When the prophylactic therapy is unsuccessful and bleeding episodes continue, synovitis may cause pain and loss of motion and radiosynovectomy can be effective in managing patients' symptoms. Surgical synovectomy, with or without radial head resection, is limited to patients with persistent synovitis after appropriate conservative management. Elbow arthroplasty can produce benefits in patients with advanced degenerative disease with an improvement of elbow pain and function at the cost of an increased rate of complications.

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6.2 Epidemiology

The elbow joint is the most common site of arthropathy after the knee joint. The exact causes of this are unknown, but the high degree of congruity of the joint and the degree of flexion-extension may produce synovial impingement at the end of motion that can produce subsequent episodes of inflammation and bleeding in a predisposed inflamed synovium after a first bleeding episode. Patients may become symptomatic at early ages (under 10) with symptoms advancing towards arthropathy in the twenties. Successful replacement factor strategies may delay these changes.

6.3 Clinical Findings

The clinical findings of patients with hemophilia are dependent on the degree of synovitis and articular damage and differ in the cases with acute bleeds and chronic symptoms from persistent synovitis and cartilage degeneration.

Patient with acute bleeds typically shows an increased joint volume with decreased and painful range of motion with an exacerbation at the end points of motion. The first episodes may start as young as 2 years of age. The skin may be shinny and show ecchymosis and other joints

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_6,

may be affected too. In first time episodes, the medical history should be directed towards the family history but usually patients have already been diagnosed by the time of their first intra-articular bleed. This first episode may produce a synovial hypertrophy if the amount of bleeding exceeds the capacity of the synovium to remove the amount of blood. This hypertrophic synovium is very vascular, so little trauma may produce new episodes of hemorrhage and perpetuate and enhance the hypertrophy of the synovium so some patients may show repetitive cases of bleeding with acute synovitis.

Patients with chronic symptoms usually show impingement signs at the end of the arc of motion probably due to impingement of the anterior synovium in flexion and the posterior synovium in extension. It is yet unclear whether the cartilage degeneration is due to chemical mediators from an inflamed synovial tissue or arises from direct chemical damage from the contact with blood, but cartilage damage may be observed in cases with more recurrent bleeding episodes.

Patients show limitation of forearm rotation, pronation being affected the first, which can decrease significantly their overall function. Degenerative changes of the elbow joint start at the radiocapitellar side with marked hypertrophy of the radial head.

As the ulnohumeral joint degenerates, the flexion-extension arc is restricted and activities against resistance in this plane of motion may become painful. Some patients may show signs of ulnar neuritis due to secondary compression due to chronic synovitis. Patients with more advanced symptoms usually show a valgus alignment of the elbow with subluxation of the radial head and marked widening of the trochlear notch with marked pain and stiffness of the elbow joint.

6.4 Radiological Findings

The radiological findings can be divided into five stages for the Arnold-Hilgartner classification with progressive joint involvement, although a modified classification leaving out stage II is frequently used [1]. This classification may guide treatment and stages III and lower can salvage the joint. Petersson et al. developed another classification ranging from 0 to 13 points (best to worse) where they evaluated the degree of osteoporosis, enlargement of the epiphysis, irregularity of the subchondral surface, narrowing of the joint space, formation of subchondral cysts, erosions at the margins of the joint, incongruence between the surfaces of the joints, and deformity of the joint considering the most affected joint of the elbow, usually the ulnohumeral joint [2] (Figs. 6.1, 6.2, and 6.3). It is somehow cumbersome for daily practice, but using three items (narrowing of joint space, irregular subchondral surface, and erosion of joint margins) can be fairly reliable. However, plain radiographs are unable to show all the lesions produced by the disease and more advanced imaging techniques are recommended [3].

Magnetic resonance imaging (MRI) and ultrasound may show marked signs of synovial hypertrophy in radiologic stages I and II. High-quality MRI may show the different degrees of cartilage erosion in stages II and III and can be decisive to make a correct indication for surgery. Specifically, MRI is the most useful technique to detect persistent synovitis and joint effusion and is particularly useful to detect early degrees of arthropathy [4]. MRI has increased costs and a combined method of radiographic and ultrasound follow-up may be a feasible alternative.

6.5 Management

6.5.1 Conservative Management

Conservative management predates any form of surgical management of elbow hemophilia. Primary pharmacologic prophylaxis is the treatment of choice as it may reduce the chance of having the first hemorrhagic episode that can start the cascade of synovial hypertrophy with increasing risk of subsequent bleeding episodes. Delaying prophylactic treatment has

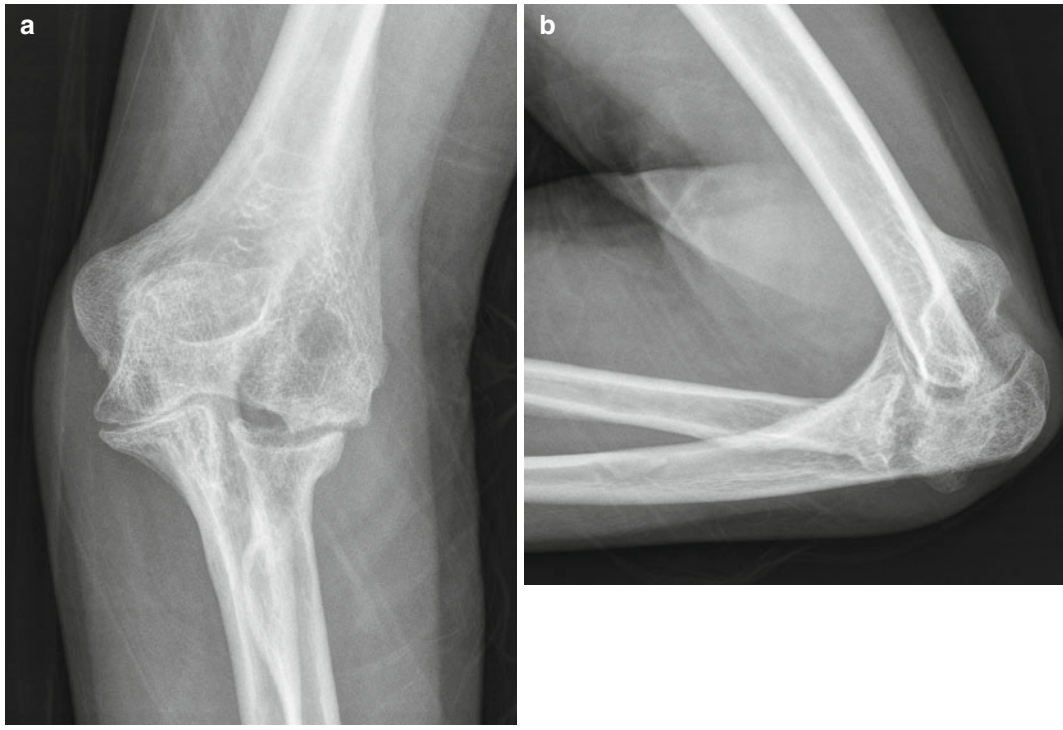

Fig. 6.1 Anteroposterior (**a**) and lateral (**b**) radiograph of the elbow showing slightly decrease of the joint line width, subchondral cysts, and mild widening of the trochlear notch (corresponding to a grade III in the Arnold-Hilgartner classification)

shown in a definite deterioration in radiological scores for every year after the first joint bleeds [5]. The forms of prophylaxis may vary from weekly injections to full form treatment that may require a central venous access, and the choice has to be made depending on patient and attending to center factors, including cost issues.

When a bleeding episode ensues, all efforts are directed towards aggressive medical treatment of major hemorrhages and chronic hemophilic synovitis to prevent hemophilic arthropathy. Other conservative measures such as radiosynovectomy with different chemical agents have been very effective in the treatment of persistent synovitis. Physiotherapy is important in managing these patients to prevent flexion deformities and maximizing range of motion.

The range of surgical options in the hemophiliac elbow depends on the degree of symptoms and pathology. Persistent synovitis after adequate medical treatment is subject to synovectomy which can be performed open or arthroscopically. Many patients with chronic synovitis may have radiocapitellar degeneration and an associated radial head removal can be performed. Only patients with persistent pain and loss of function and severe destruction of the joint are candidates for total elbow replacement.

6.5.2 Synovectomy

It is yet unclear if there is a direct relationship between synovitis and cartilage degeneration or if the cartilage is in fact directly affected by the contact with blood, but synovectomy may be indicated with persistent symptoms of synovitis with no response to conservative measures. It seems that synovectomy is an appropriate treatment to

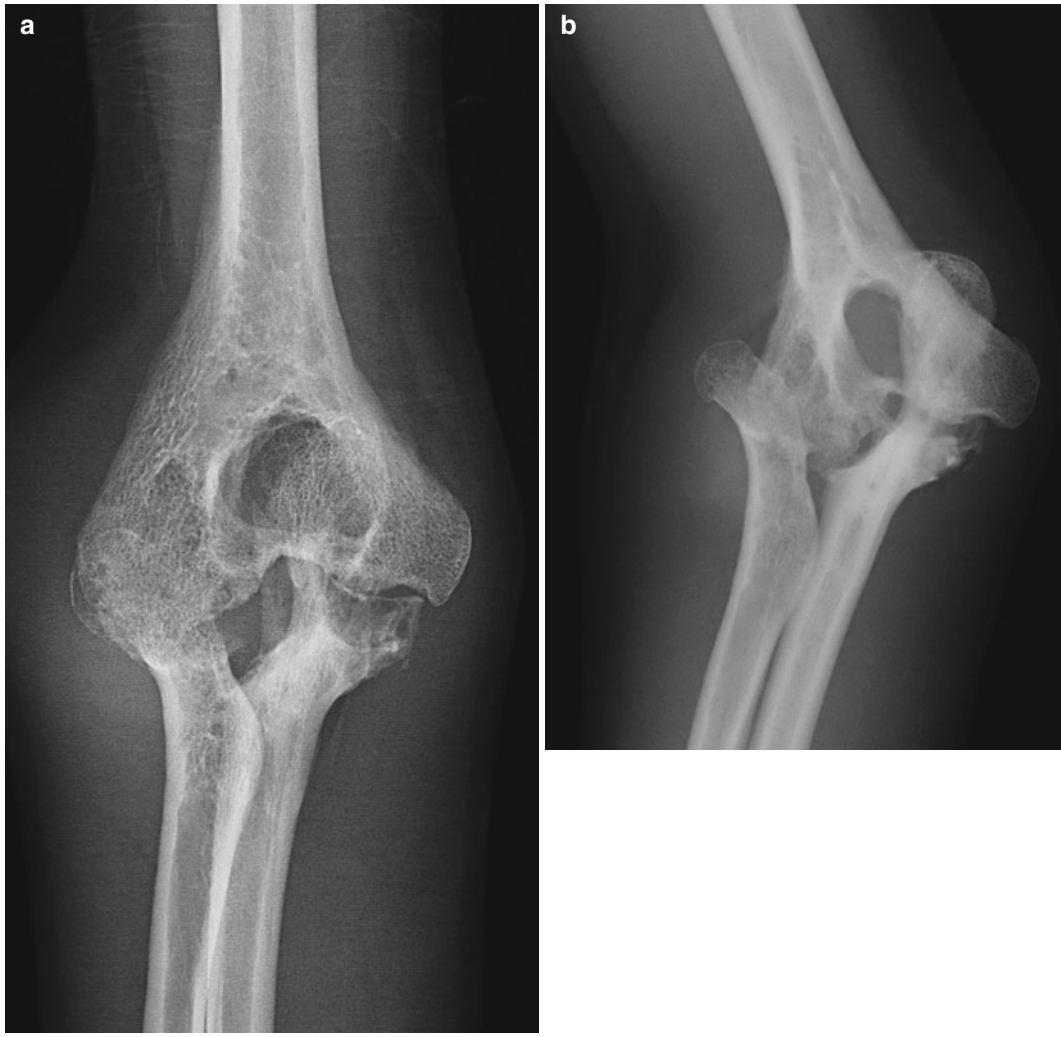

Fig. 6.2 Anteroposterior (**a**) and lateral (**b**) radiograph of the patient in Fig. 6.1 5 years later. The articular surface is narrowed and the widening of the trochlear notch is increased. The radiocapitellar joint is the first part of the joint to show signs of the disease

delay joint degeneration, more so if performed early [6].

While the incidence of bleeding is significantly decreased after surgical synovectomy, it is not necessarily associated with a cessation of the progression of joint pathology. Reduced incidence of bleeds following postsurgical synovectomy may serve to delay reconstructive operations until a later period in life. Eventually, the disease proceeds to end-stage arthropathy and joint function correspondingly decreases with age. Patients should be managed conservatively with therapeutic doses of factor concentrate replacement for a reasonable period of time in an effort to avoid surgical treatment [7].

Indication for Synovectomy

The senior author (ECR-M) favors using radiosynovectomy in children older than 12 years of age, arthroscopic synovectomy in patients under that age, limiting open surgery for adults requiring radial head removal due to severe limitation and synovectomy in the same surgical session [8]. However, recent advancements in surgical

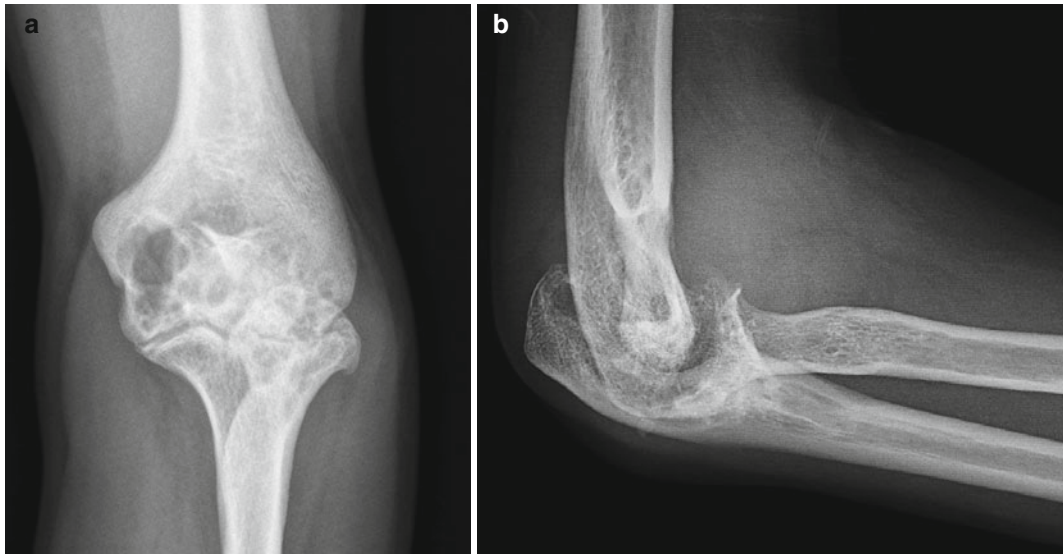

Fig. 6.3 Anteroposterior (**a**) and lateral (**b**) elbow radiographs with marked hypertrophy of the radial head that limited forearm pronation. Additionally, some signs of advanced hemophilic arthropathy can be seen

technique and instrumentation have fostered the use of arthroscopic surgery as a valuable tool in the treatment of these patients [9].

Open Surgical Synovectomy

Patients are positioned supine with the arm resting on an arm rest. The limb is exsanguinated and a Kocher approach to the elbow is used. The interval between the anconeus and the extensor carpi ulnaris is identified by palpation or identification of a fat strip in the distal part of the interval. The dissection is carried out to the capsule and it is incised just anterior to the lateral collateral ligament. Working with the forearm in pronation increases the safe distance to the posterior interosseous nerve. If a radial head resection is to be performed, Hohmann retractors are placed around the radial neck and a subcapital osteotomy using an oscillating saw is performed. The axis of the neck cut should be perpendicular to the axial alignment of the radius and the height should be just distal to the lesser sigmoid notch. Synovectomy is easily performed with dedicated rongeurs through the space provided by the radial head resection including the anterior and posterior aspects of the joint. If access to the posterior part of the joint is limited, extension of the elbow and slight elevation of the triceps may improve the exposure.

If the radial head is not resected, access may be limited by the presence of the radial head. Extending the approach proximally may facilitate synovectomy of the hypertrophied synovial tissue. In these cases, it is probable that an arthroscopic technique increases our ability to remove all the diseased tissue.

Osteophytes limiting flexion and extension should be removed and waxed to prevent postoperative bleeding. Standard closure is performed with interrupted closure of the forearm fascia with a deep suction drain. A compressive dressing is applied with a posterior plaster splint in 90° elbow flexion and supination is applied.

Arthroscopic Synovectomy

We place patients in the lateral decubitus with the affected arm on a dedicated arm holder and under tourniquet control. We insufflate the joint with saline through the soft spot to facilitate introduction of the arthroscope. Our first portal is a proximal anteromedial portal. Patients should be assessed preoperatively as to the existence of ulnar nerve subluxation. If this is the case, we perform an anterior transposition of the nerve

through an open approach and then proceed to the arthroscopic synovectomy.

Our second portal is an anterolateral portal performed with an outside-in technique and it should give access to remove all the disease synovium in the anterior compartment by exchanging viewing and working portals. Synovectomy is achieved with the use of a motorized shaver. Posterior synovectomy is used through a mid-triceps portal, an accessory lateral portal, and a soft spot portal. If there is bony impingement, bone resection with a burr can be achieved. The portals are closed with horizontal mattress sutures over a drain placed in the posterior compartment. Postoperative indications are similar to the open technique.

Results of Synovectomy

Le Balc'h et al. reported their results in 23 elbows in 18 patients in young patients (mean, 14 years of age) with a severe deficiency (>1 %) with a minimum follow-up of 18 months. The indication for surgery was recurrent episodes of bleeding despite substitutive treatment for each episode, mainly with lateral elbow pain. The age was related to the degree of pain. An increase in motion was observed in 23 elbows (pronosupination in 9 elbows and flexion-extension in 14 elbows). Four patients reported recurrent bleeding episodes and pain persisted in three. They reported the use of radial head removal in the oldest patients (the oldest being 25 years old) if radiocapitellar wear was present and considered the presence of inhibitor a contraindication to the procedure [10].

Pietrogrande et al. described their short-term experience using open synovectomy in three cases due to failure to control the incidence of hemarthrosis with persistent synovitis. Synovectomy reduced but not abolished the incidence of hemarthrosis, but episodes were usually less severe and incapacitating. Joint mobility was reduced after surgery despite prolonged physiotherapy although patients were usually satisfied due to an increase in the activity they could lead because of a decreased number of bleeds [11].

Kay et al. reported on the use of elbow synovectomy in 12 elbows with a minimum 1-year follow-up for the indication of recurrent bleeding episodes not responding to adequate factor replacement therapy. The number of bleeding episodes went from 24 episodes per year to three episodes per year with complications occurring in 25 % of the cases. Six patients gained a mean of 11° of flexion-extension arc while five patients lost an average of 28° [6].

Verma et al. reported the results of arthroscopic synovectomy of the elbow in a group of patients with persistent synovitis after medical treatment. The authors state that arthroscopy has the benefit of performing an effective synovectomy while at the same time being able to debride intra-articular adhesions, capsular release, and osteophyte resection. A significant improvement in pain and range of motion and function and a decrease in the number of bleeds were observed at last follow-up [9].

6.5.3 Total Elbow Arthroplasty

Most modern authors have used total elbow arthroplasty (TEA) for the management of advanced hemophilic arthropathy although there is limited experience with the use of interposition arthroplasty as a salvage surgery without the use of implants. Smith et al. used a sheet of silicone rubber as an interposition membrane after a limited excision arthroplasty in six patients. They reported no complications and reported an increase in function and pain relief. Additionally they showed a reduced rate of hemorrhage episodes after the index procedure [12].

Butler-Manuel et al. used silastic interposition arthroplasty in severe hemophilic arthropathy in thirteen cases with a 5-year follow-up. Patients improved in pain and function. They reported three complications, one for infection and two due to failure of the silastic implant at a minimum of 5-year follow-up. However, these patients underwent successful revision surgery [13].

Total Elbow Arthroplasty

Total elbow arthroplasty is used for grade III–IV hemophiliac arthropathy which includes changes in the axial alignment of the limb, so linked

elbow arthroplasty is the implant of choice. Patient satisfaction is generally high specifically for pain relief, but patients should be advised that implant survival is less than for other indications and complications are increased when compared to other indications, specifically infection and loosening [14]. Almost all authors have used a hinged (TEA) in the more modern studies. Anecdotally, Street and Stevens reported their use of a metallic hemiarthroplasty of the trochlea and capitellum in two cases of ankylosed elbows after hemophiliac disease with unpredictable results [15].

Surgical Technique

All of these patients have to undergo adequate factor replacement surgery perioperatively to control perioperative episodes of hemorrhage. These procedures are performed under tourniquet control and appropriate hemostasis throughout the procedure. The patients are usually placed supine and a posterior skin incision with ulnar nerve dissection and anterior transposition is used. The triceps can be managed as desired but adequate space to perform the anterior and posterior capsulotomies and synovectomies and bony cuts to implant the arthroplasty are developed. Our preference is to use antibiotic-loaded cement to fix the arthroplasty. A semi-constrained linked implant is our choice as good functional outcomes can be expected [16]. Good attention to implant alignment is critical as it will probably reduce the stress on the arthroplasty interface and help improve the longevity. After standard closure, the elbow is placed in a well-padded cast in extension and elevation to limit bleeding.

Results of Elbow Arthroplasty

Chapman-Sheath et al. reported their results using a (TEA) in seven cases for five consecutive patients with severe hemophilia A after a mean follow-up of 42 months. All patients obtained excellent pain relief and more modest gains in function. The authors report one infection in an inmunocompromised patient with HIV and HCV antibodies on antiretroviral drugs. They revised the implant using one-stage procedure 30 months after the index surgery and showed no evidence of loosening or infection 35 months after the revision surgery [17].

Marshall Brooks et al. reported their experience using seven (TEAs) in six patients for severe factor VII and IX deficiency (four and two patients, respectively). Mean age at the time of surgery was 34 years of age with a mean follow-up of 118 months. At a mean of 19.2 months, range of motion was improved in five of seven cases with modest gains both in flexion (from 111° preoperative to 120° postoperative) and extension (44° preoperative to 37° postoperative). At 118 months, all implants were functioning with reduced pain and preserved function with ability to perform normal daily activities. One patient required a revision surgery at 30 months' postoperatively for ulnar component loosening, and the same patients underwent an excision arthroplasty for a *S. epidermidis* infection 15 years' postoperatively [18].

Sorbie et al. analyzed the long-term results of the Sorbie-Questor implant, an unlinked surface arthroplasty, implanted between 1995 and 2005 for hemophilia, rheumatoid arthritis, and other indications, including posttraumatic conditions. The patients with hemophilic arthropathy showed the greatest survival rate of all the groups with an 87.5 % survival rate at long-term follow-up. These patients showed an increase in flexion-extension arc of the elbow and decreased pain. The authors concluded the long-term effectiveness of the procedure [19].

Wang et al. reported their experience using bilateral total elbow arthroplasty (TEA) in three patients with a mean follow-up of 3 years. The MEPS (Mayo Elbow Performance Score) showed good or excellent results in five of the six arthroplasties. The authors showed an increase in patient complications and modest functional gains with good pain relief [14].

Kamineni et al. reported on the use of a linked elbow implant in five cases with grade III and IV hemophilic arthropathies, all being HIV positive [16]. The patients improved their MEPS from 24 points preoperatively to 90 points postoperatively. At final follow-up, all arthroplasties were in place except one that had to be removed 2 months' postoperatively after infection. Of note, three out of five patients had a complication, two of them requiring

a reintervention. One patient with an inhibitor had an acute hemorrhage and developed wound necrosis and a deep infection by Bacillus species. The implant had to be removed, and wound coverage with a flexor carpi ulnaris flap and split thickness skin graft eventually healed the wound. There was another infection 4 years' postoperatively due to an hematogenous *Staphylococcus aureus* that was treated with debridement, removal of the linking mechanism, an antibiotic spacer, and intravenous antibiotics for 2 months with reimplantation of the prostheses after the inflammatory markers returned to normal and survival of the implant thereafter. Another patient had persistent pain but more localized and did not require reintervention. Two patients showed radiolucent lines, and one of them could be classified as an aseptic loosening with progressive radiolucent lines but did not require a reintervention.

Conclusions

Appropriate management of elbow problems in hemophilic patients includes coordinated care with an emphasis in adequate preventive measures. If conservative management of bleeding episodes fails, synovectomy, with or without radial head removal, decreases the number of bleeding episodes and improves function, specifically forearm rotation. Total elbow arthroplasty is reserved for the more advanced arthropathy cases that are willing to comply with postoperative restrictions, but it improves pain management and function at the cost of an increased rate of complications.

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Hip Surgery in Hemophilia

7

Eduardo García-Rey and Eduardo García-Cimbrelo

7.1 Introduction

Although the knee is the most frequent joint to be affected in hemophilic arthropathy, the epiphyses of the femoral heads undergo typical changes that severely disable these patients. A recent study from the Universal Data Collection database reported that the prevalence of clinical abnormalities in the hip is related to the severity of the hemophilia, the type of the inhibitor concomitant ankle arthropathy, age, and obesity [1].

Different authors published the first case reports in the 1930s describing radiographic changes in some hips. Winston described the pathology in the hemophilic hip in a series of seven patients [2]. He emphasized three important findings: the importance of the appearance of hip pathology before or after puberty, the proper description of the mechanism of the pathology, and the possible relationship to other joint disorders. Before then Löhr had reported the flattening and irregularities observed in the hip epiphyses of children due to hemorrhages and weight bearing [3]. Probably, the intraepiphyseal hemorrhage is the most important contributor to damage and collapse, although the different patterns observed also suggest that the degree of damage is the result of a combination of the severity and the sites of the hemorrhages [2]. In the young adult, femoral head collapse is not frequent and cyst formation and arthritic changes are similar to degenerative primary osteoarthritis. These patients also frequently present a certain degree of bone density loss.

The mechanism behind avascular necrosis in hemophilia remains unclear [4]. It has been suggested that the occlusion of the epiphyseal vessels could be the cause of necrosis due to hemarthrosis [4, 5]. Paton and Evans observed an absence of pain in a series of three patients with necrosis and they thought this could be explained by the absence of significant hemorrhage [6]. They suggested that mild trauma and the defect in blood coagulation resulted in bleeding into the joint after the damage to the critical irrigation of the femoral head. Pettersson et al., after reviewing the clinical and radiological findings in patients before or after the era of factor therapy introduction, observed that there were typical characteristics of Legg-Calvé-Perthes disease, suggesting that hip joint bleeding and the subsequent distension increased intracapsular disease [7]. Different deformities occur in the proximal femur including a small femoral canal, malalignment, and torsional disorders. To date, poor bone quality is associated with acetabular protrusio and the frequent contractures, producing fibrosis which limits the normal function of the hip.

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_7,

7.2 Management of Hip Hemophilic Arthropathy

Recent years have shown that the continuous prophylaxis in developed countries can decrease the number of episodes of bleeding and their complications; however, the musculoskeletal disorders, particularly arthropathy, continue to present problems, even in young patients.

Although different surgical treatments have been reported, like synovectomy, particularly for other joints, for the hip, total hip arthroplasty (THA) provides the best clinical outcome for most patients and improves their quality of life [8].

Anesthesia is another issue for these patients. Although a spinal regional block can be performed after the proper preoperative hematological control, most surgeries are being done under general anesthesia. Factor substitution is critical before and after surgery. Bellingham et al., in one of the first cases, reported the safety of a cemented hemiarthroplasty using a prophylactic therapy with cryoprecipitate in a 21-year-old male patient who had sustained a femoral neck fracture [9]. With the proper medical management, significant bleeding in the perioperative period is not frequent and is usually similar to patients undergoing THA due to other causes. Hematological monitoring is done until wound healing, usually 2 weeks.

As in other degenerative hip pathologies, femoral osteotomies attempt to relieve pain and improve functional ability for these patients; however, results are not conclusive in hemophilic arthropathy [10]. The good results reported for THA in hemophilic patients need to be evaluated, particularly in some aspects [11].

Augereau et al. reported a very low rate of complications in 13 cemented arthroplasties [12]; however, later studies have reported inferior results in these patients than in non-hemophilic THAs mostly due to the young age and other hemophilic-related factors, such as human immunodeficiency virus (HIV) infection [13–15]. Most authors agree that a higher infection rate and aseptic loosening rate can be expected than in patients diagnosed with primary osteoarthritis who undergo THA. The use of factor as prophylaxis could reduce the incidence of asymptomatic bleeding around the implants and the appearance of loosening in the cement-bone interface [15]. THA has also been demonstrated to be a useful procedure for spontaneous ankylosed hips in patients diagnosed with hemophilia [16]. Sikkema et al. reported in a matched case-control study showed similar results for patients with and without bleeding disorders, so with proper medical and surgical management, success can be expected for THA in hemophilic patients [17].

Although cemented fixation has been recommended due to poor bone quality, cementless fixation is being used. Habermann et al. reported no failures when using hybrid or cementless THA, so, although they initially used cemented THAs in hemophilic hip arthropathy, they recommended cementless implants that provide good long-term results for these young patients since no aseptic or septic loosening has been observed [18]. Later, Yoo et al. also reported the good results of cementless THA in a series of 27 hips with a minimum follow-up of 5 years; there were only two failures due to wear and cup loosening [19] (Fig. 7.1). Due to these reasons, alternative bearing surfaces are being used in order to decrease long-term wear-related problems as is done in other conditions [20]. Our current recommendations for THA in these young hemophilic patients are cementless fixation and an alumina-on-alumina bearing surface [21] (Fig. 7.2).

Revision hip surgery remains a challenge for the orthopedic surgeon, particularly when a major bone defect is present [22]. Thus, young age of hemophilic patients is another concern regarding the best reconstruction for their hips. The incidence of this surgery is increasing since better medical management has been developed and physical activity remains a

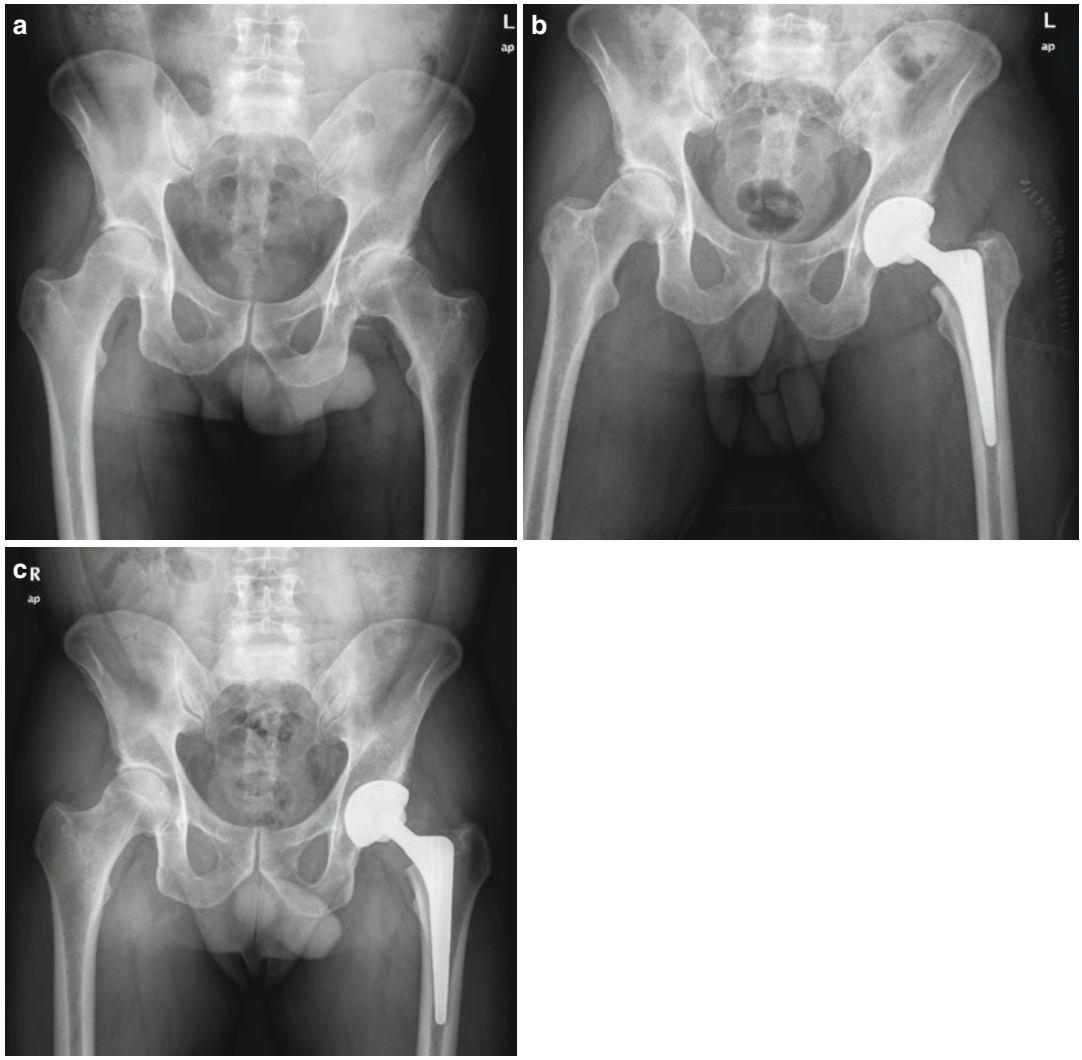

Fig. 7.1 (**a**) Preoperative radiograph of a 49-year-old patient with hip hemophiliac arthropathy. An osteopenic acetabulum and a funnel-shaped femoral canal can be observed. (**b**) Radiograph of the same patient at the first postoperative week with a cementless press-fit cup and a cementless stem. The bearing surface is an alumina-on-alumina couple. (**c**) Radiograph of the same patient done during the second postoperative year. Note the radiological signs of osteointegration of both acetabular and femoral cementless components

higher level than some decades ago. Management of bone loss is the most critical issue in these young adult patients, and impaction grafting, for both acetabular and femoral sides, is one of the best options for these patients [23, 24] (Fig. 7.3)

7.3 Muscular Disorders of the Hip in the Hemophilic Patient

Other characteristics of the pathology that affect the musculoskeletal system in hemophiliac

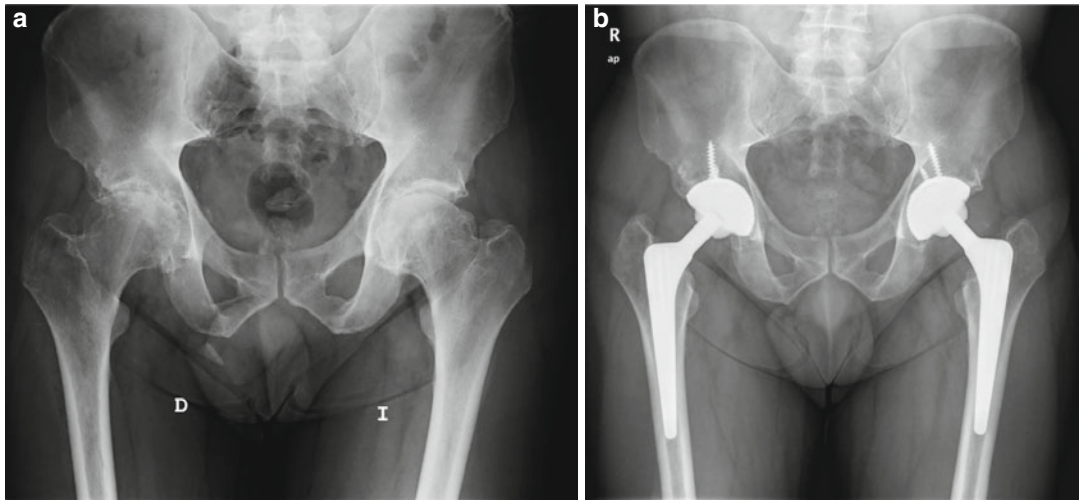

Fig. 7.2 (**a**) Anteroposterior pelvic radiograph of a 56-year-old male patient showing hemophilic arthropathy of both hips. Note deformity in both femoral heads, osteopenic acetabulum, and dysplastic cylindrical femur. (**b**) Anteroposterior pelvic radiograph during the third and second postoperative year after bilateral alumina-on-alumina cementless total hip arthroplasty of the same patient. These cementless cups needed screw for a proper primary fixation

patients are muscular disorders. Goodfellow et al. described a series of 24 patients diagnosed with classical hemophilia with the typical symptoms of iliacus hematoma [25]. Pain in the groin in the absence of a significant trauma was the most important finding, and it could be acute or insidious. Flexion contracture in external rotation with preservation of movements of the hip joint but extension was also other frequent sign. Another finding observed was femoral nerve palsy due to compression and a mass in the iliac fossa.

The appearance of muscle hematomas can be spontaneous, and hematological treatment is required before further complications develop [26]. Since this process may take several weeks, a hemophilic pseudotumor can develop due to the appearance of new bleedings. This finding can be the source of new disorders in the musculoskeletal system, and because it may destroy bone and soft tissue, resection can become very difficult, particularly for a pelvic pseudotumor [27]; however, with proper management including a multidisciplinary approach, a satisfactory outcome can be obtained. A typical site for hematomas in patients with hemophilia is within the iliopsoas muscle [28]. The anatomy and size of this muscle motivate the large volume of the mass, and, to date, muscular and femoral nerve involvement has been frequently reported, as well as re-bleeding. Groin pain and contractures are frequently seen, and management of a hematoma can be conservative: rest, physical therapy, and long-term hemostatic therapy. However, the clinician must be alert to the possibility of muscular affectations in order to prevent complications. Ultrasound-guided percutaneous drainage is a current option before surgery for some hematomas, although recurrence is still relatively frequent [29]. At the long term, the appearance of heterotopic ossification can develop into a myositis ossificans that will affect the joint function and may necessitate surgery.

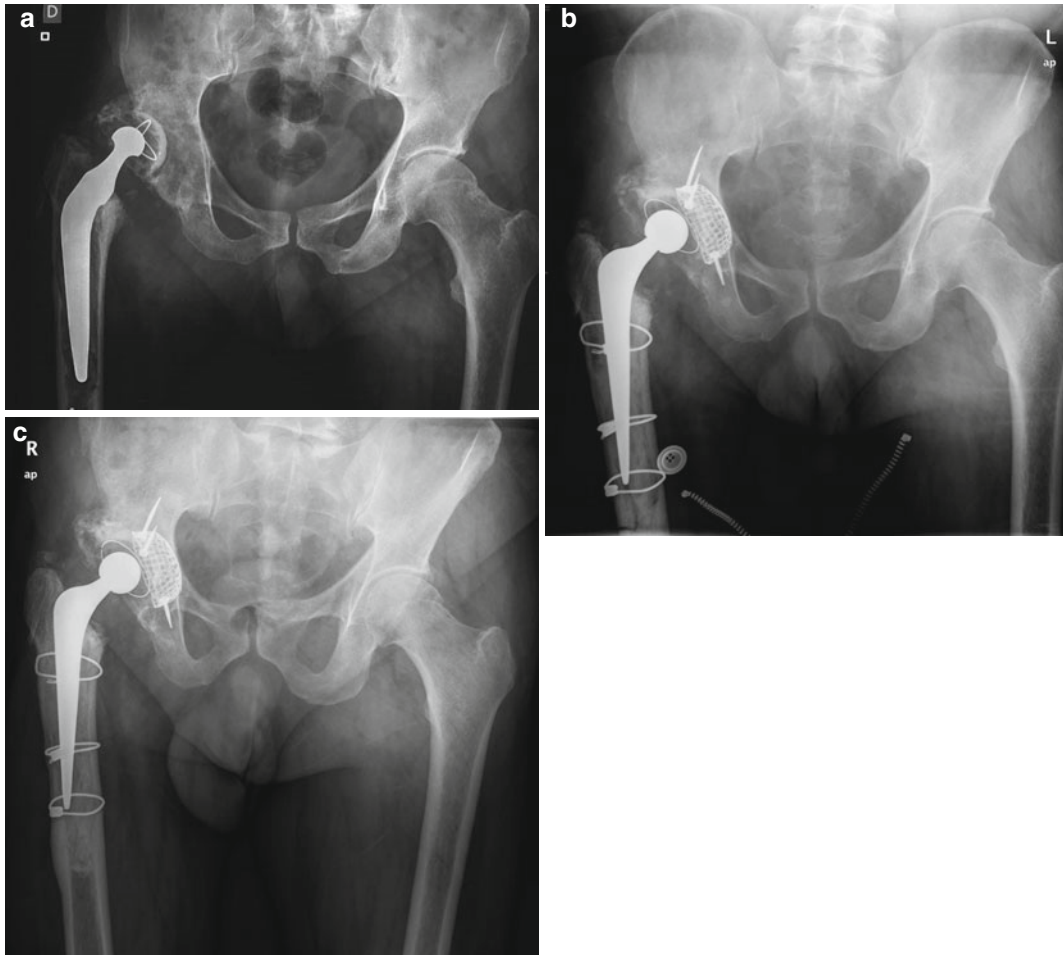

Fig. 7.3 (**a**) Radiograph showing aseptic loosening of a cemented low-friction arthroplasty of a 62-year-old hemophilic patient at the tenth postoperative year. There was an intraoperative segmental and cavitary bone defect in both acetabular and femoral sides. (**b**) Sixth postoperative week radiograph of the same patient after reconstruction hip surgery with impaction bone grafting and cemented implants. A medial mesh was needed in the acetabulum prior to grafting and an extended femoral osteotomy in the femur to remove the implant and the cement. (**c**) Second postoperative year radiograph of the same patient. Bone remodeling and stable fixation can be observed on both acetabular and femoral sides

Conclusions

Although hip affectation is relatively rare in hemophilia, when it occurs it generally requires a THA to safeguard their mobility and quality of life. Current implants and alternate bearing surface may improve clinical and radiological outcome of these patients. While hip pain and functional impairment are usually due to arthropathy, hemophilic patients can also present muscular disorders with similar symptoms and can produce serious complications. These patients require close monitoring by a multidisciplinary team to successfully manage the musculoskeletal affectation of the hip.

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Knee Surgery in Hemophilia

8

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8.1 Introduction

Orthopedic knee problems are very frequent in hemophilia. Taking into consideration the significant hematological progress in handling hemophilia (primary prophylaxis) in recent decades, for a long time now, we have thought and hoped that orthopedic surgeons would no longer be necessary in the treatment of the frequent knee problems that patients with hemophilia suffer. Unfortunately, to this time, that wish has not come true. In the 40 years that we have been working on the musculoskeletal problems of the knee in hemophilia, we have never stopped operating to resolver multiple problems, from the simple draining of a hemarthrosis (joint aspiration or arthrocentesis) to performing a total knee replacement (TKR), whether primary or for revision.

In this chapter, we will analyze orthopedic knee problems in hemophilia and the surgical techniques that can be used to relieve these problems. What we present as follows are concepts based on 40 years of experience, which have provided relief to the knees of hemophiliac patients.

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8.2 General Concepts

In some countries (20–30 % of the world population), the orthopedic problems of hemophilia have reduced since the prophylaxis of the disease was introduced in them [1]. In this way, in these countries, they have managed to turn serious hemophilia into a milder type of hemophilia, maintaining the factor level above 1 % permanently [2]. This achievement has not been easy, due to the enormous economic problem it represents, as well as the difficulty in achieving intravenous lines in patients with hemophilia (catheter infection, repeated vein punctures from early childhood, etc.). Patients in primary prophylaxis can even enjoy sporting activities similar to those performed by the general population [3].

Other developed countries do not use the abovementioned prophylaxis in its primary form (i.e., starting at 2 years of age before the appearance of the first hemarthrosis) but rather its secondary form (i.e., starting it as decided by each hematologist at a slightly later age, when some hemarthrosis have already occurred).

The huge economic cost of primary prophylaxis means that 70–80 % of the world's hemophiliac population does not have access to that treatment; what is more, some regions of the world do not even have access to the on-demand treatment, that is, the deficit factor replacement therapy when a hemorrhagic episode occurs (hemarthrosis).

We live in a world in which we know quite a lot about the ideal treatment of the disease, but in which

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_8,

we cannot always carry it out. In Spain, the health authorities do not restrict the treatment of people with hemophilia, and nowadays, hemophiliac children display a much better musculoskeletal situation than 40 years ago; however, the children of that time are now adults, who, despite being lucky enough to have survived the HIV epidemic, suffer serious articular knee complications, which often require an orthopedic surgeon. The most problematic patients are those who develop inhibitors, although we can now perform orthopedic knee procedures on them with a high success rate [4].

In hemophilia, it is essential to carry out an individual treatment plan for each patient. In the case of a surgical procedure, the hematological standard must be extremely careful, whereby it is the hematologist's mission to assess the benefit of treatment in bolus or in continuous infusion. In other words, the multidisciplinary team basically formed by a hematologist, orthopedic surgeon, rehabilitation physician, pediatrician, psychologist, physiotherapist, and a nurse is essential for the correct treatment of musculoskeletal knee problems in the hemophiliac patient.

These problems represent 80–90 % of the problems that people with hemophilia suffer throughout their lives. This means that the orthopedic surgeon's role is still essential in the context of a multidisciplinary team [5].

Sometimes it may be recommendable to perform double or triple surgery in one surgical act, in order to resolve the patient's functional problem globally (due to the fact that the pathology is usually polyarticular). Undoubtedly this increases the risk of anesthesia, although, on the other hand, it can produce savings in the clotting factor and avoid repeated surgeries [6]. All surgery must be carried out with intravenous antibiotic prophylaxis for 24–48 h and under the supervision and treatment of a hematologist who controls the hemostasis correctly.

8.3 Articular Puncture (Drainage of Hemarthrosis)

An articular knee puncture is a simple but very effective procedure, which can be performed as an outpatient or in the patient's bed. For that reason, we believe it is reasonable to include articular puncture in this article as an orthopedic procedure. Articular punctures allow tension hemarthrosis to be drained [4, 7–9]. Ultrasonography is very useful in diagnosing hemarthrosis and also in confirming its total disappearance after the suitable treatment, that is, after on-demand hematological treatment at the appropriate intensity and duration, associated with the drainage of the hemarthrosis [10].

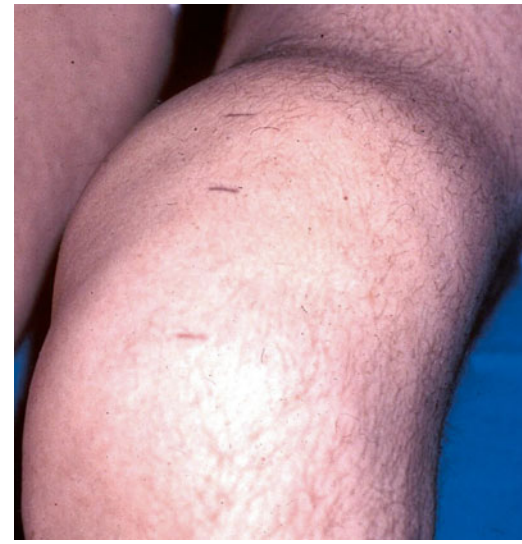

Fig. 8.1 Clinical image of intense chronic synovitis in a young hemophiliac patient. The problem was treated by radiosynovectomy with Yttrium-90

8.4 Synovectomy

After recurrent hemarthrosis, the hemophiliac patient's knee reaches a state of chronic synovitis (synovial hypertrophy), which in turn perpetuates the tendency towards new bleeding (Fig. 8.1). The clinical diagnosis must be confirmed via imaging tests [10]. Under these circumstances, this hypertrophic synovial must be resected using nonsurgical (radiosynovectomy and chemical synovectomy) or surgical procedures (arthroscopic or open synovectomy). The aim of both methods is to reduce the frequency and intensity of the hemarthrosis. Nowadays, surgical knee synovectomy is usually performed via arthroscopy [11].

In general, it is recommendable to perform a nonsurgical synovectomy before indicating any type of surgical synovectomy, given that the nonsurgical method is much simpler and easier (with similar efficacy). We use radiosynovectomy with Yttrium-90 in children over 12 years of age, and we prefer arthroscopic synovectomy in children under that age. The dose we use for knee radiosynovectomy is 185 MBq. Yttrium-90 is a pure beta-emitter, with therapeutic penetration power of 2.8 mm and an average life of 2.8 days. We have never used chemical synovectomy because it requires multiple painful weekly injections of rifampicin or oxytetracycline.

On the knee, arthroscopic synovectomy requires good perioperative hemostasis, as synovial tissue bleeds a lot. The appropriate clotting control via the infusion (continuous or bolus) of the deficit factor is essential to prevent postoperative bleeding [5]. Arthroscopic synovectomy usually requires at least two entry points in order to resect as much synovial as possible [11]. After synovectomy (of any kind), it is recommended to use a compression bandage for 3–4 days and ensure the joint has limited mobility (that permitted by the bandage).

In summary, radiosynovectomy and arthroscop ic synovectomy are effective methods to control recurrent hemarthrosis of hemophiliac knee. We always empirically use radiosynovectomy with Yttrium-90 first (1–3 intra-articular injections, with 6-month intervals between them), with 70 % satisfactory results. If after the three abovementioned radiosynovectomies, the hemarthroses continue, we would prescribe an arthroscopic synovectomy.

8.5 Handling Knee Flexion Contractures

In patients with knee flexion contractures, as long as the joint is conserved (i.e., there is no marked arthropathy), it is recommendable to firstly carry out conservative treatment based on progressive extension serial casting or a progressive extension orthosis. When this conservative method fails, it is recommendable to perform tendon lengthening that allows appropriate articular extension and, hence, better function of the affected joint. On the knee, this is achieved by lengthening the tendons of the popliteal fossa (hamstrings release) associated with the posterior capsulotomy [5]. Such procedures must be performed when the contractures are moderated and the conservative treatment has failed.

For the treatment of knee flexion contractures, and with the aim of achieving progressive extension, external fixators can also be used (such as the Ilizarov circular fixator). Fitting a fixator requires a surgical procedure with very complex postoperative recovery. In the case of a fixator for progressive extension, its extending device must be handled with care, to achieve a maximum extension of approximately 30° in 1 month (a daily grade). Subsequently, the fixator must be removed and an orthosis fitted that ensures the extension gained is maintained and even improved. What this procedure achieves is a slow but progressive extension of the periarticular soft tissues (including tendons, vessels, and nerves). Abrupt lengthening could cause a paresis of the peroneal nerve.

8.6 Articular Arthroscopic Debridement

The arthroscopic debridement of the knee is usually performed on adult patients with severe arthropathy of the knee who are considered too young for TKR (these prostheses have an average life of 10–15 years). In short, it is a procedure that can relieve articular pain and bleeding for some years, and which delays the need for a TKR. An articular debridement consists of the resection of the existing osteophytes, in the extirpation of the synovial and in the curettage of the articular cartilage of the femoral condyles, tibial plateaus, and patella. Some authors do not believe in this procedure's effectiveness, and they consider that in cases of severe knee arthropathy, it is better to go directly to TKR, even in young patients. If the debridement fails, TKR can always be performed [5, 11]. Postoperative rehabilitation is essential as we must prevent loss of mobility, through appropriate control of the hemostasis and physiotherapy with a suitable protocol (in order to prevent postoperative bleeding).

8.7 Alignment Osteotomy

On certain occasions, during childhood or early adulthood, some hemophilic knees present alterations of their normal axes. It is common for the knees to present varus, valgus, or flexum attitudes, depending on each case. When the misaligned joint is symptomatic, the patient may benefit from realignment osteotomy. The most common are the valgus proximal tibial osteotomy, the varus femoral supracondylar osteotomy, and the knee extension osteotomy [5]. After the osteotomy, the bone will have to be fixed with some kind of osteosynthesis device. It is interesting to point out that we have sometimes taken the opportunity to correct a contracture in preflexion of the knee while treating a supracondylar femoral fracture. Once again, postoperative rehabilitation is essential to maintain mobility in the aligned joint. When the axial deviation occurs in a patient with intense and incapacitating arthropathy in whom it is indicated to perform a TKR, during the same prosthetic procedure the prior deformity will also be corrected.

8.8 Total Knee Replacement (TKR)

In the adult hemophiliac patient, TKR is the most common prosthetic procedure, and it is indicated when the pain and the functional incapacity are intense [5, 12–18]. It is sometimes advisable to operate on both knees at the same time, in order to achieve the correct function of the lower limbs. Other times it is preferable to first operate on the most painful joint and then the other (after 6 months).

Most TKR are variants of what was originally called total condylar prosthesis. The procedure is usually performed with ischemia of the member via a straight longitudinal incision and an internal para-patellar line. It is advisable to perform it with ischemia and bone cement with antibiotics. On completion of the implant, it is recommended to release the ischemia cuff to perform the best hemostasis possible. Suction drainage is normally fitted as well as a compressive knee bandage for 24–48 h. It is recommended to use intravenous antibiotic prophylaxis during 24–48 h (cefazolin 1 g every 8 h).

After 24–48 h, the drainage and intravenous antibiotic prophylaxis are removed, so that by the third day, the patient starts the postoperative rehabilitation. The patient is usually hospitalized for 7–10 days. The aim is for the patient to leave the hospital on foot with the help of walking sticks, with a knee flexion of 90° and total extension of the joint. The stitches or staples are usually removed after 2–3 weeks. The results of TKR in hemophilia have been quite satisfactory thus far (Fig. 8.2). Therefore, TKR is considered a good procedure in cases of severe knee arthropathy [5, 14–20]. The results are nearly comparable with those of osteoarthritis patients, and it can even be performed on patients with inhibitor [4]. However, the risk of infection is higher in hemophiliac patients than in the population with degenerative arthritis (osteoarthritis): average 7 % versus average 1 % (Fig. 8.3).

Taking into account that a large proportion of our adult patients are HIV positive, they can be immunologically compromised with a view to surgery. Furthermore, most of them are also hepatitis C virus (HCV) positive. That is, there may be a certain risk of postoperative infection if an immunosuppressed hemophiliac patient is operated on. In actual fact, there is great controversy regarding this issue, as while some authors indicate quite a high risk of postoperative infection in patients with less than 200 CD4, others have not found such a high level of infection [21, 22]. What is clear is that immunosuppression in some way increases the risk of postoperative infection and that the patient must be informed of this risk; the risk is even higher in prosthetic surgery, as inert material is implanted (the prosthesis). Current immunodeficiency treatments mean that patients

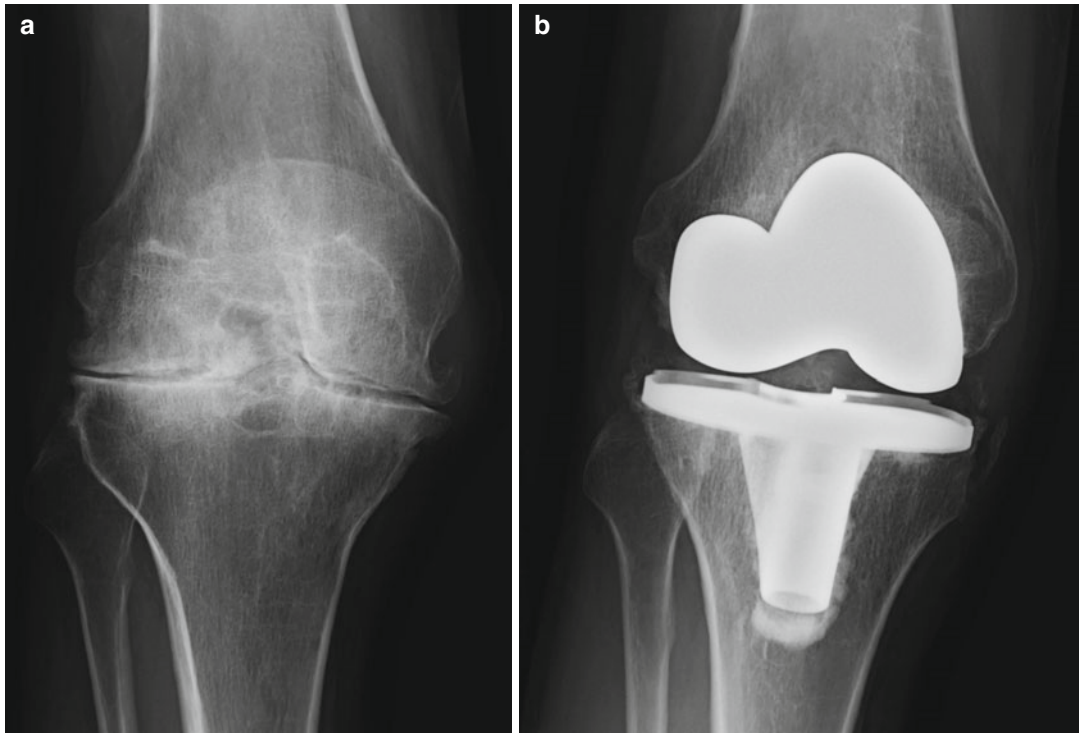

Fig. 8.2 Severe arthropathy of the knee (**a**) resolved satisfactorily with an unconstrained primary total knee replacement (TKR) (**b**)

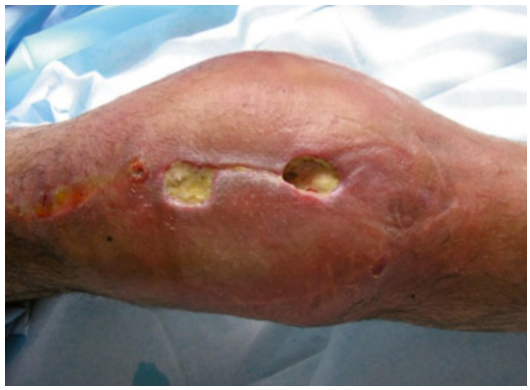

Fig. 8.3 Clinical image of severe postoperative infection in hemophiliac patient after total knee replacement (TKR)

reach the surgery in good immunological condition. As always in medicine, the proper risk/benefit analysis is essential in each particular case.

The type of prosthesis to implant will depend on the level of preoperative stability, whereby it may even be necessary to implant rotating-hinge prosthesis in cases of extreme instability (Fig. 8.4). That is, the degree of constriction of the TKR will increase in line with the degree of preoperative instability of the knee [23].

Another possible complication is the forming of a postoperative arterial pseudoaneurysm, which usually causes intense bleeding (hemarthrosis) [17]. The problem is normally resolved via the early arterial embolization of the blood vessel (Fig. 8.5). As we mentioned earlier, the average life of a TKR is usually 10–15 years, which is why many hemophiliac patients require a prosthetic knee revision, for which the results are also satisfactory, although to a lesser extent than the primary prosthesis (Fig. 8.6).

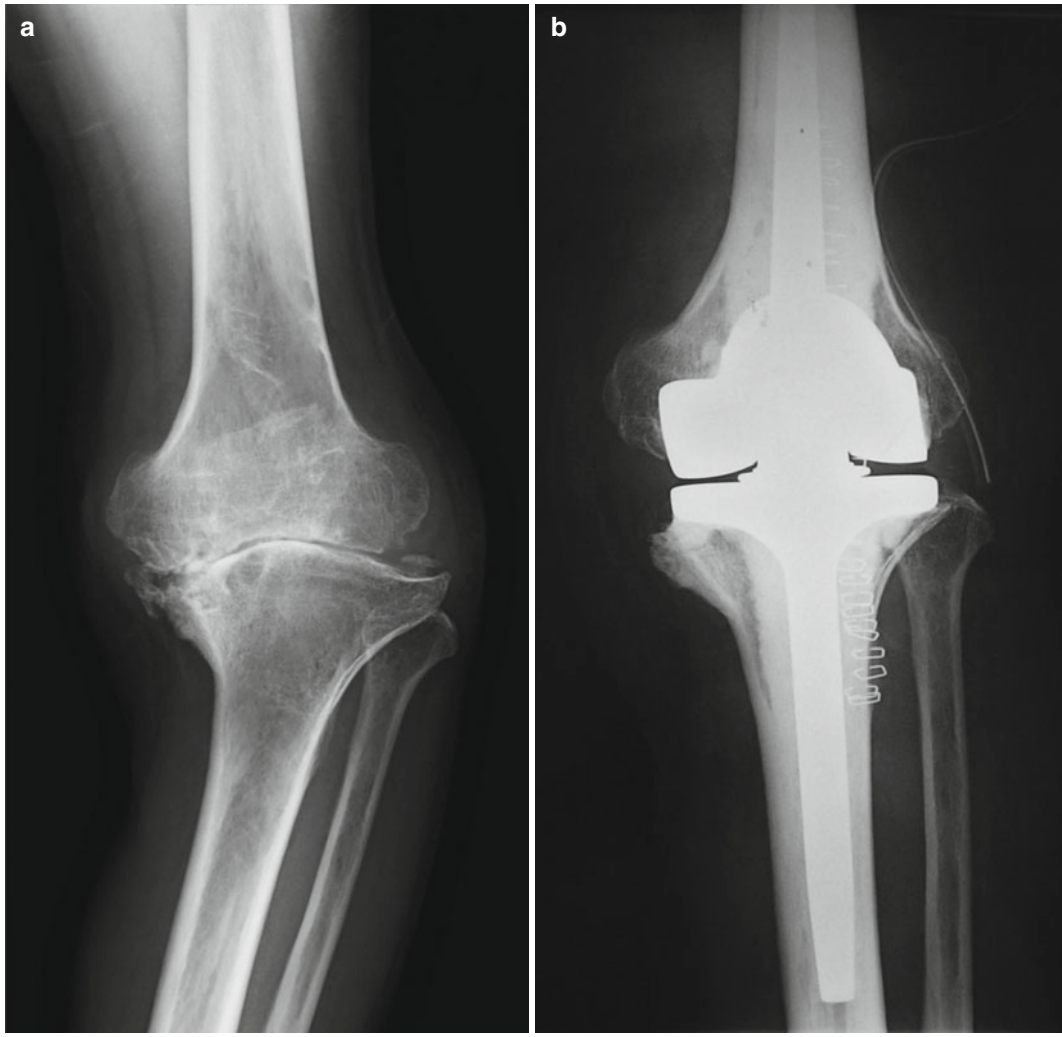

Fig. 8.4 Advanced arthropathy of the knee with intense varus deformity and preoperative instability (**a**) which was treated satisfactorily using a constrained rotating-hinge total knee prosthesis (TKR) (**b**)

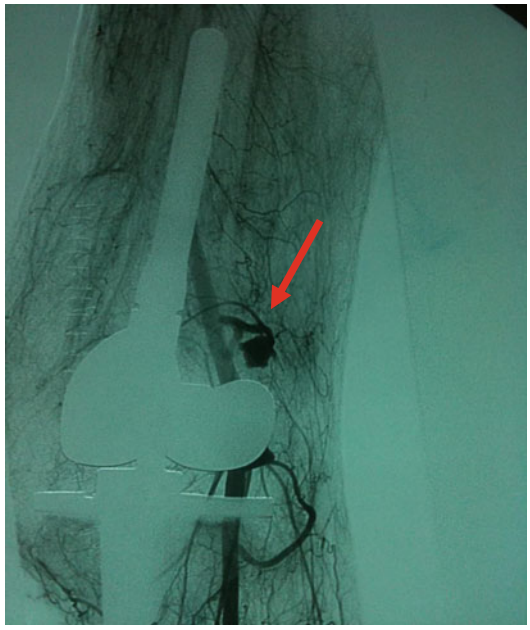

Fig. 8.5 Pseudoaneurysm (*arrow*) detected 6 days after the implant of a semi-constricted total knee replacement (CCK, constrained condylar knee) in patient with marked preoperative valgus deformity who presented intense hemarthrosis on the operated knee. It was resolved satisfactorily via early arterial embolization

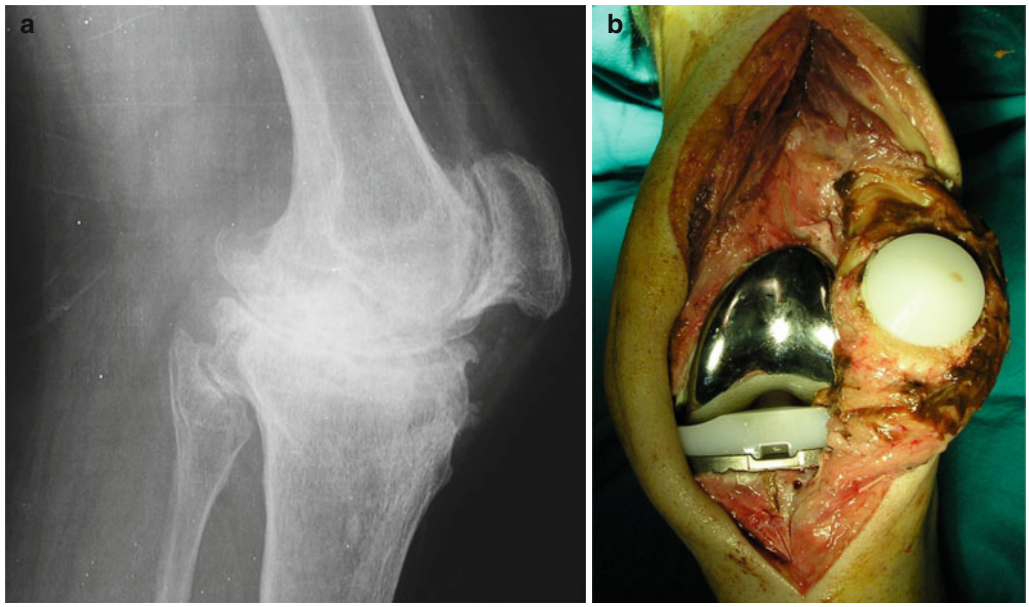

Fig. 8.6 Painful and incapacitating advanced arthropathy of the knee in adult hemophiliac patient who required a total knee replacement (TKR). The result was satisfactory. Eleven years later, the prosthesis had to be revised due to aseptic loosening. (**a**) Radiological image before the prosthesis. (**b**) Intraoperative image of the satisfactorily implanted prosthesis. (**c**) X-ray before the revision procedure, showing clear signs of loosening. (**d**) Radiological image after the prosthetic revision

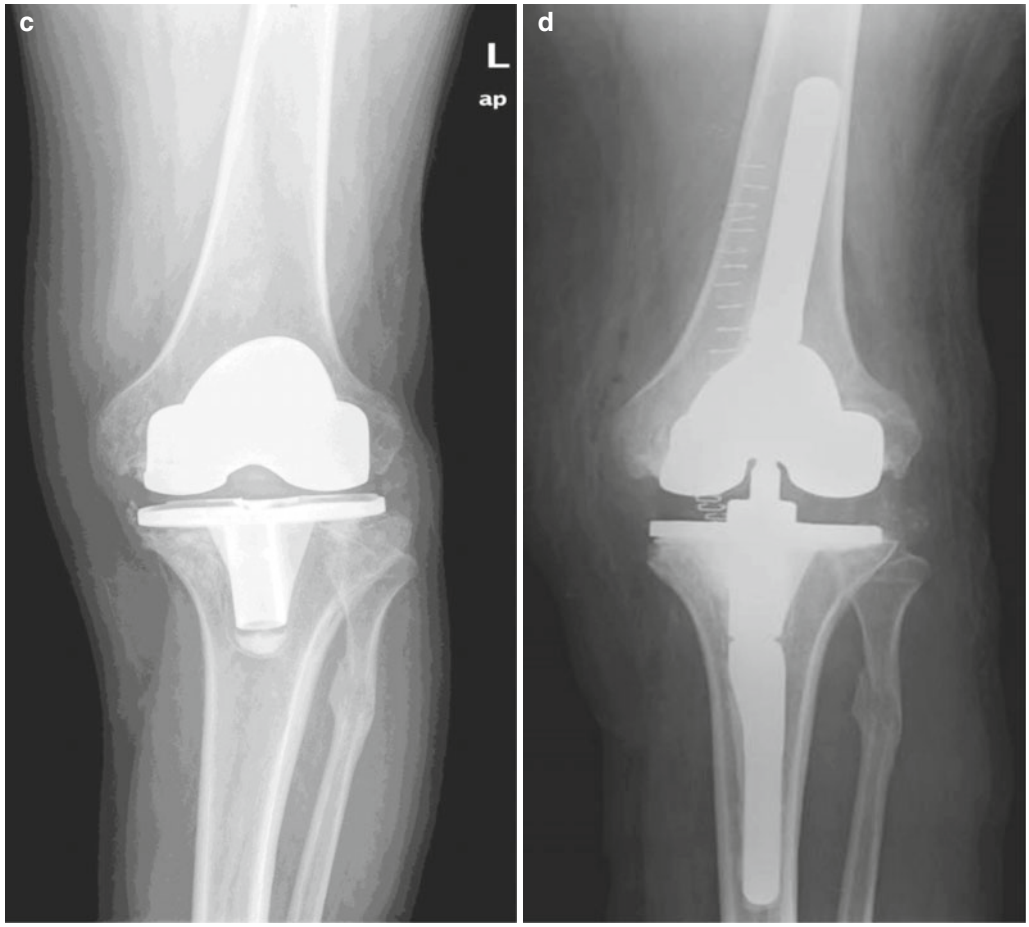

Fig. 8.6 (continued)

Conclusions

Until we manage to avoid orthopedic complications of the knee in the hemophiliac patient via primary hematological prophylaxis, orthopedic surgeons will have to continue performing articular punctures (arthrocentesis) to drain the hemarthrosis, radiosynovectomies, arthroscopic synovectomies, hamstrings release, arthroscopic debridement, alignment osteotomies, and TKR (primary or for revision, with different degrees of constriction) on the knees of people with hemophilia. With this, we will achieve an improvement in the quality of life of hemophiliac patients who suffer orthopedic knee problems.

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9 Advanced Hemophilic Arthropathy of the Ankle: Total Ankle Replacement or Ankle Fusion?

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9.1 Introduction

In the final stages of hemophilic arthropathy of the ankle, when the joint is severely destroyed and the intense joint pain and/or major functional disability do not respond to nonsurgical treatment (hematological prophylaxis, analgesics, anti-inflammatories, orthotics), we must consider the need to carry out surgical treatment to alleviate the patient's problems [1–4].

Among the surgical techniques for the treatment of ankle joint destruction in idiopathic degenerative disease, before reaching the elimination of the joint via arthrodesis or total ankle replacement (TAR), we can try to relieve the symptoms by using the following surgical techniques [5]: arthroscopic ankle debridement (Fig. 9.1), joint distraction (arthrodiastasis) using external fixation, or supramalleolar osteotomy for alignment (in cases with particularly bad alignment).

However, in some patients, none of these techniques sufficiently alleviates the problem, leading us to consider the elimination of the joint via arthrodesis (joint fusion) or TAR. Today there is much controversy, both in the general population and in hemophilia patients, about which technique is most advisable. The purpose of this article is to review the literature on arthrodesis and TAR in non-hemophilia population, as well as in hemophilia patients, to try to clarify the controversy over arthrodesis or TAR.

9.2 Search Strategy

In a literature search for articles published in English in PubMed (MEDLINE) that included from January 2000 to December 2013, we found 43 articles related to ankle arthrodesis and TAR in non-hemophilia patients and in hemophilia patients. Another three articles on survival of knee prosthesis (TKR) and hip replacements (THR) were included for comparison with the ankle prosthesis (TAR). The keywords used were hemophilia, ankle, arthrodesis, and TAR. In total 46 articles were analyzed.

9.3 Results of TAR and Arthrodesis

In 2005, Stengel et al. [6] published a systematic review and meta-analysis (included in the Cochrane Library) on the effectiveness of TAR on the general population. In 1,086 patients, 35.2

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DOI 10.1007/978-3-319-10780-6_9,

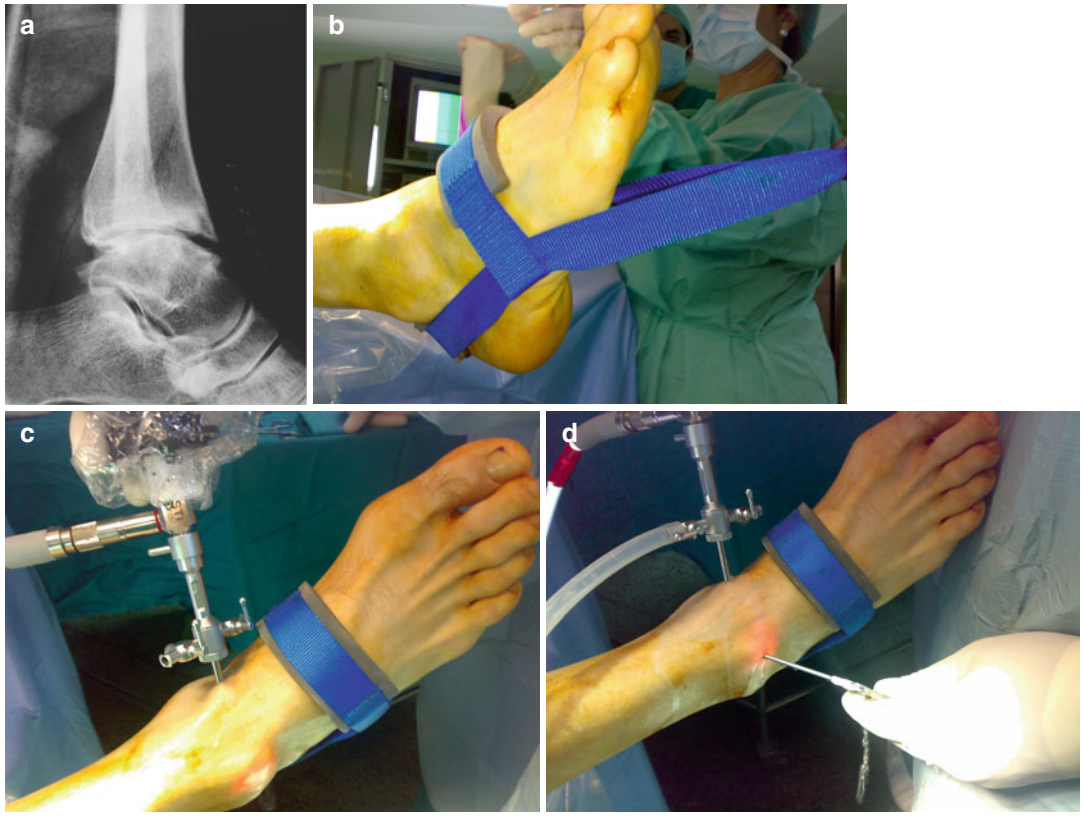

Fig. 9.1 Arthroscopic debridement of the ankle in a patient with advanced hemophilic arthropathy: preoperative lateral radiograph (**a**). Traction device used for the procedure (**b**). Anteromedial and anterolateral portals used to perform debridement (**c**, **d**)

complications were found (1.6 % deep infections, 14.7 % impingement, 12.5 % secondary surgery, 6.3 % secondary arthrodesis). The prosthetic survival at 5 years was 90.6 %.

In 2011, in another systematic review, included in the Cochrane Library, Zhao et al. [7] analyzed 2,088 TARs with an average follow-up of 52 months. The failure rate was 11.2 %, whereby almost half of them occurred in the first year (5.2 % due to aseptic loosening, 1.7 % due to misalignments and 1 % of infections). The prosthetic survival at 5 years was 85.9 % and at 10 years was 71.1 %.

Also in 2011, Mann et al. [8] analyzed 84 TARs (in 80 patients), achieving a level of satisfaction with the result of 92 %. At an average of 9.1 years, 91 % of the TARs were still in place. They had a 25 % complication rate (including 14 secondary surgeries). The prosthetic survival at 5 years was 96 % and at 10 years was 90 %. Hendrickx et al. [9] analyzed 66 ankle arthrodesis (in 60 patients) with an average follow-up of 9 years, achieving a fusion rate of 91 %. There were seven (10 %) complications (six re-arthrodesis, one infection). 91 % of patients were satisfied with the result. Progressive osteoarthritis was detected in the adjacent joints, although its importance is still unknown.

In 2012, in another article, included in the Cochrane Library, Roukis et al. [10] analyzed 2,312 TARs with an average follow-up of 22.8 months. 9.7 % of them (224) had to be revised, leading to new prostheses in 182 cases (81.3 %), 34 in arthrodesis (15.2 %), and 8 in amputation below the knee (3.6 %).

In 2013, Noelle et al. [11] analyzed 100 TARs performed on 97 patients with an average

follow-up of 36 months. They had 27 complications and needed 21 revisions. Gordon et al. al [12] studied 82 ankles (73 patients) on which open ankle arthrodesis was performed using the anterior approach. 100 % of cases fused, with an average fusion time of 13.3 months. 80 % of patients were very satisfied or satisfied. The complication rate was 14.6 % (malalignment, healing problems, complex regional pain syndrome, delayed fusion).

A controversial topic regarding ankle arthrodesis is whether it should be tibiotalar (TT) or tibiotalocalcaneal (TTC). Ajis et al. [13] analyzed 100 TT arthrodesis, and they compared them with 173 TTC arthrodesis, with an average follow-up of 63 months (minimum 24 months). There were no differences in the results as regards three of the parameters studied: preoperative pain relief, return to previous work (74 %), and whether patients would be operated again (83 %), the results were similar. However, there was a difference in the desired level of activity, which was 58.5 % in TT arthrodesis and 66.5 % in TTC arthrodesis.

One of the most striking complications of TAR is periprosthetic fractures. In 2013, Manegold et al. [14] reported a rate of 4.2 % (2.2 % intraoperative, 2 % postoperative).

A controversial issue is the revision of the TAR when it fails. Hinterman et al. [15] in 2013, presented 117 TAR revisions (in 116 patients), noting that the survival of the prosthetic revision was 83 % after 5 years, with similar results to those of primary TAR. There were 19 complications (16 %) highlighting 1 malleolar fracture, 1 dislocation of the prosthetic polyethylene, and 15 secondary revision surgeries.

It should be noted that although ankle arthrodesis is usually performed as an open procedure [1–5], it can also be carried out by arthroscopy. In fact, Lee et al. [16] in 2011 and Townshend et al. [17] in 2013 stated that arthroscopic ankle arthrodesis has better fusion rates, fewer complications, less postoperative pain, and a shorter hospital stay than open arthrodesis.

9.4 Comparative Studies: TAR vs Arthrodesis

In 2009, Saltzman et al. [18] noted that TAR provides better function than arthrodesis; however, from the pain perspective, the relief is comparable. Their study (included in the Cochrane Library) compared 158 TARs and 66 ankle arthrodesis, with an average follow-up of 24 months.

Noelle et al. [11] obtained a similar complication rate between TAR and arthrodesis. In an ongoing study, Flavin et al. [19] noted a clear improvement after either procedure (TAR or arthrodesis) with similar postoperative results.

In a comparative study published in 2012 by Schuh et al. [20], in which TARs (20 cases) and arthrodesis (21 cases) were compared with an average follow-up of 34.5 months, the authors found no differences in sports, recreational activities, and function.

According to Terrell et al. [21], the number of TARs increased by 57 % from 2004 to 2009, although the number of ankle arthrodesis did not change in that time period. However, as the previously studied literature highlights, prosthetic survival of the TAR (Table 9.1) is far from that of hip replacements (THR, total hip replacement) and knee (TKR, total knee replacement) [22–26]. TAR survival at 14 years is 62 %, while that of THR is 93 % and 88 % at 15 and 20 years, respectively [27]. TKR survival is somewhat less than that of THR, 84 % and 71 % at 10 and 20,

Table 9.1 Survival rates for total ankle replacement (TAR) in the general population according to literature (2005–2013)

Author	Survival at 5 years (%)	Survival at 10 years (%)	Survival at 14 years (%)
Stengel [6]	90.6	–	–
Zhao [7]	85.9	71.1	–
Mann [8]	96	90	–
Henricson [22]	81	69	–
Pinar [23]	86	–	–
Barg [24]	94	84	–
Brunner [25]	–	70.7	45.6
Angthong [26]	–	–	77

respectively [28, 29]. Obviously there are no TAR survival studies with over 14 years of follow-up. Our opinion coincides with that of Henricson et al. [22], who stated that TAR survival will not come close to that of THR and TKR in the near future in the population with advanced ankle arthrosis. We must not forget that TAR currently presents a high complication rate, failures, and revision (Table 9.2). In comparative studies, Saltzman et al. [18] indicate better function after TAR but equivalent pain relief. Schuh et al. [20] found no difference between TAR and arthrodesis as regards sports, recreational activities, and function. Flavin et al. [19] did not find any differences in postoperative progress either. Thus, even the literature with a high level of scientific evidence does not clarify the controversy over TAR or ankle arthrodesis, but it does state that TAR has not reached the levels of survival of THR and TKR.

Table 9.2 Rates of complications, failures, and revision for total ankle replacement (TAR) in the general population according to literature (2005–2013)

Author	Complications (%)	Failures (%)	Revision (%)
Stengel [6]	35.2	–	–
Mann [8]	25	–	–
Zhao [7]	–	11.2	–
Angthong [26]	–	4.9	–
Henricson [22]	–	–	22
Roukis [10]	–	–	9.7
Noelle [11]	27	–	21
Barg [24]	–	–	8.4
Brunner [25]	–	–	38

9.5 Total Ankle Replacement (TAR) or Arthrodesis of the Ankle in Hemophilia

According to Ling et al. [30], the incidence of arthropathy is very high in hemophilia patients, whereby 47 % of them were in pain and 52 % had positive radiological signs. In hemophilia, patients with ankle arthropathy present a modification in progress that improves recovery via the pendular mechanism, in order to save energy. This modification is proportionately greater in cases of greater arthropathy [31].

Before considering surgery, in severe hemophilic arthropathy of the ankle nonsurgical treatment including hematological prophylaxis, analgesics, anti-inflammatory, rehabilitation, and functional orthoses should be attempted [1–5, 32–34]. A surgical alternative used on only three hemophilia patients is arthrodiastasis (joint distraction) via circular external fixator by Ilizarov [34]. An alternative is supramalleolar osteotomy for realignment mentioned by Pearce et al. [35] who performed seven such interventions on six hemophilia patients.

As regards the controversy over TAR or ankle arthrodesis in hemophilia (Figs. 9.2, 9.3, and 9.4), back in 1976, Zimbler [36] mentioned the

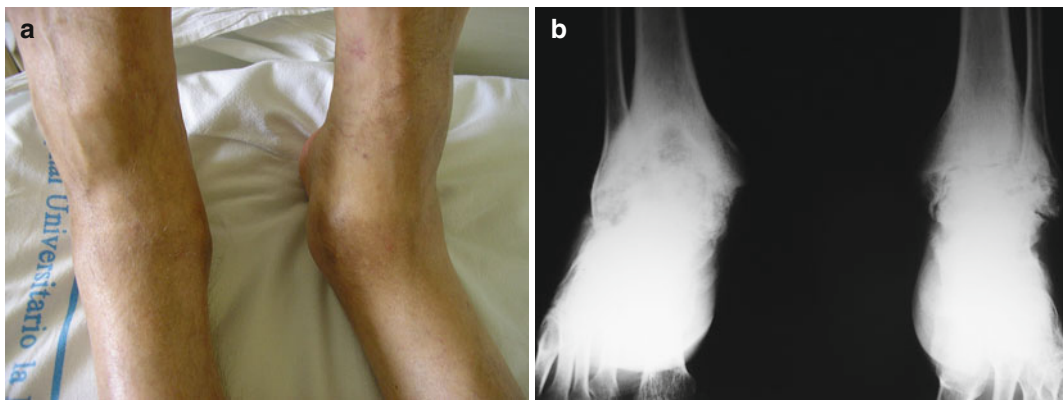

Fig. 9.2 Right ankle arthrodesis with a retrograde locking nail in a patient with severe hemophilic arthropathy of the tibiotalar and subtalar joints: preoperative view of the ankles (**a**). Anteroposterior radiograph of the ankles before surgery (**b**)

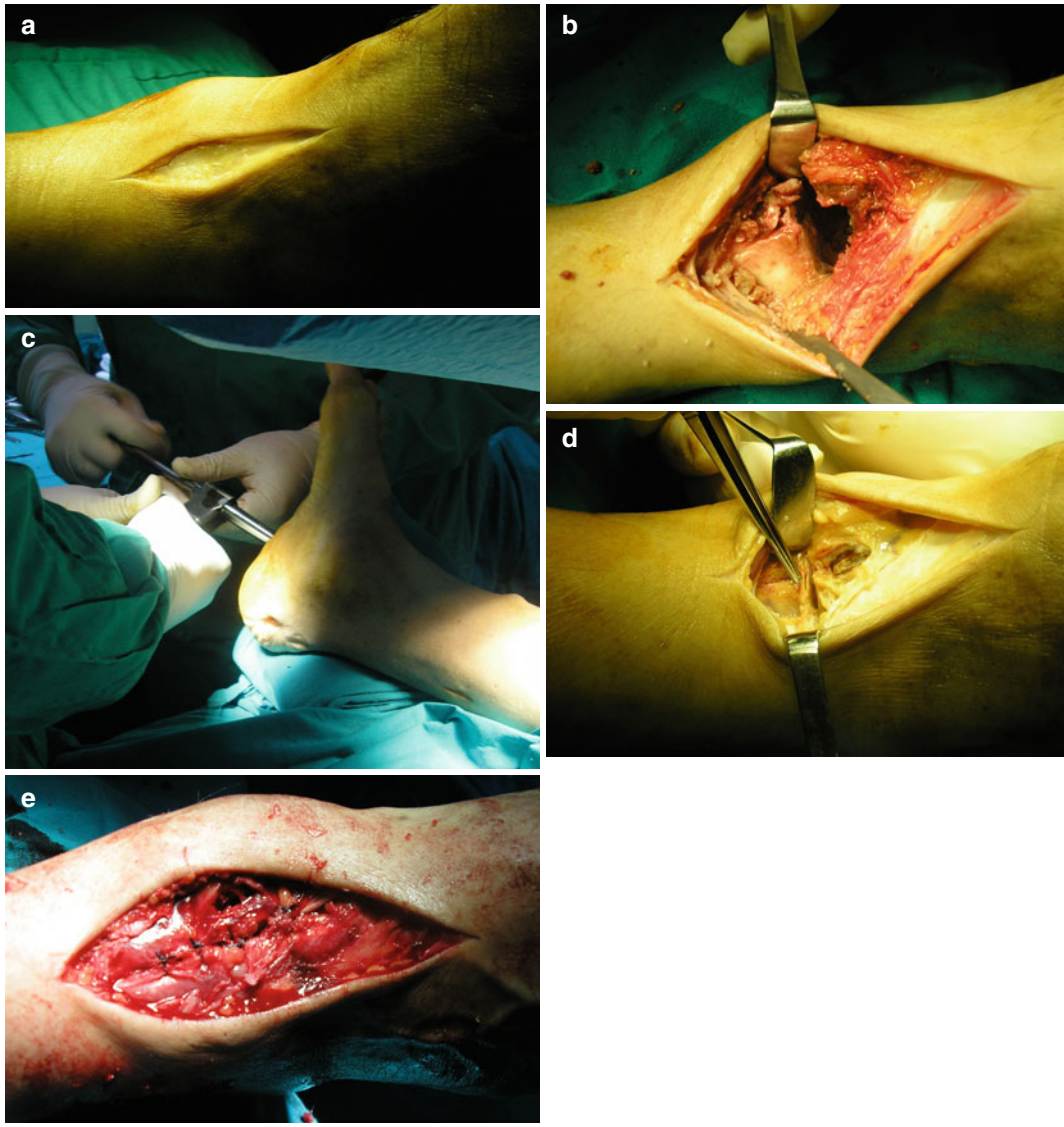

Fig. 9.3 Right ankle arthrodesis with a retrograde locking nail in a patient with severe hemophilic arthropathy of the tibiotalar and subtalar joints: intraoperative images of the procedure (**a–e**)

possibility of using TAR in these patients. In 1978 Houghton et al. [37] published seven ankle arthrodeses in hemophilia with satisfactory results. In 1991 Gambler et al. [38] noted that in elderly hemophilia patients, arthrodesis eliminates pain and bleeding, improving the deformity.

As regards ankle arthrodesis, in 2010, Tsailas and Wiedel [39] published 20 arthrodeses (in 13 patients with an average age of 38.7 years), 11 of them ankle (tibiotalar), 1 subtalar, and 8 combined. Average follow-up was 9.4 years. In 2011, Tsukamoto et al. [40] presented three arthroscopic ankle arthrodeses in two patients with hemophilia. In 2013, Bluth et al. [41] presented 54 ankle arthrodeses with an average of 6.6 years (in 45 patients). There was tibiotalar nonunion in 10.4 % of patients and subtalar nonunion in 8.3 % of them, but no further surgery was required. Their conclusion is that arthrodesis is a suitable surgical treatment. The ankle arthrodesis technique described in 2009 by Mann et al. [42] is of interest.

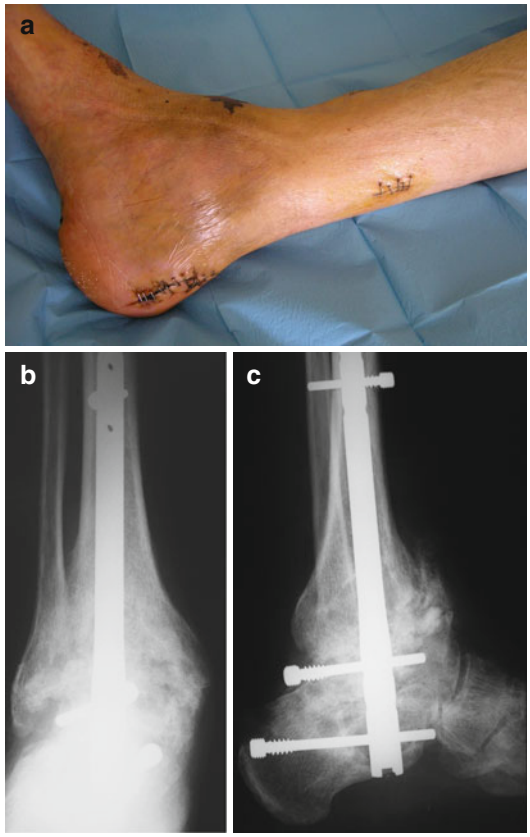

Fig. 9.4 Right ankle arthrodesis with a retrograde locking nail in a patient with severe hemophilic arthropathy of the tibiotalar and subtalar joints: lateral postoperative view of the ankle (**a**). Anteroposterior radiograph after arthrodesis (**b**). Lateral view after ankle fusion (**c**)

Bai et al. reported a series of ten patients (ten ankle joints) who underwent arthroscopically assisted ankle arthrodesis for the treatment of end-stage hemophilic arthropathy [43]. The fusion rate was 100 %. The average time to fusion was 10.5 weeks. Superficial wound infection occurred in one patient. There were eight good to excellent results and two fair results. All patients were satisfied with the outcome of the operation. Arthroscopic ankle arthrodesis was an effective alternative to open technique with established advantages in hemophilic arthropathy [43].

As regards TAR in hemophilia, in 2006, van der Heide et al. [44] published five cases (in three patients) with an average of 4.3 years. In 2010, Barg et al. [45] published ten TARs in eight patients, with an average age of 43.2 years with an average follow-up of 5.6 years (minimum 2.7 years). They had only one complication (painful fibrosis that required open arthrolysis).

The literature on TAR versus ankle arthrodesis in hemophilia is very limited and has a limited degree of evidence. Therefore, the literature does not tell us which of the two techniques is most suitable in advanced hemophilic ankle arthropathy. Before TAR or arthrodesis, we should think about arthroscopic debridement [1–4], arthrodiastasis [46], or supramalleolar osteotomy for realignment [35].

9.6 Author's Experience

In a period of 40 years, the authors performed 454 orthopedic surgical procedures on 398 hemophilia patients. Of these, only six were ankle procedures: four arthroscopic debridement and two ankle arthrodesis (one tibiotalar, one tibiotalocalcaneal). To date, we have not performed any TARs given its short survival in the long term and high rate of complications. In our experience, ankle arthropathy can be sufficiently relieved in a large percentage of cases with nonsurgical treatment, and the need for surgical intervention on this joint is very rare. For us, removing the ankle joint (via arthrodesis or TAR) is always the last option: we always try arthroscopic debridement before considering arthrodesis or TAR. On the other hand, given the controversy in the literature on ankle arthrodesis or TAR and the lack of literature on the subject in hemophilia, we currently tend to prefer arthrodesis to TAR in people with hemophilia. If the subtalar joint is affected, we prefer open tibiotalocalcaneal arthrodesis with locking nail. If not, we would opt for open tibiotalar arthrodesis with crossed cannulated screws or staples.

Conclusions

The current literature concerning the controversy on ankle arthrodesis or total ankle replacement (TAR) in non-hemophilia patients

is not definitive (it does not clarify the controversy). As regards hemophilia patients, the uncertainty is even greater, as there is very little literature available. Based on all of this and on our 40 years of experience treating people with hemophilia, our advice is to exhaust all types of nonsurgical treatment. When surgical treatment is considered absolutely necessary, my recommendation is to conserve the joint at all costs using arthroscopic debridement, arthrodiastasis, or supramalleolar osteotomy for realignment, according to each surgeon's preferences. If these techniques fail, when in doubt on whether to perform arthrodesis or TAR, in hemophilia, we would always opt for arthrodesis, as the current results for TAR quite frankly have much room for improvement. It is likely that in the mid-long term, new TAR designs will allow these results to improve.

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Articular Pseudotumors and Bone Cysts in the Adult Hemophilic Patient

10

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and Eduardo J. Ortiz-Cruz

10.1 Introduction

Pseudotumors and bone cysts are a serious, but very rare, complication in hemophilia. The hemophilic pseudotumor is an encapsulated hematoma. They may arise from bleeding into muscle, under periosteum, or into the bone. Once established, the pseudotumor has a tendency to progress and produce clinical symptoms by mass effect in relation to its anatomical location, leading to bone and soft-tissue lesions, or neurovascular complications.

In 1965, Fernández de Valderrama and Matthews [1] described a hemophilic pseudotumor as a progressive cystic swelling involving muscle, produced by recurrent hemorrhage and accompanied by radiographic evidence of bone involvement. In a review of his experience at Oxford, in 1966 Gunning [2] estimated its incidence to be about 1 % of all severe hemophiliacs.

The majority all reported hemophilic pseudotumors involve the musculoskeletal system. A few intra-abdominal pseudotumors have been reported, but these were in fact tumors of the pelvis that had extended into the abdomen [3, 4]. Seldom retroperitoneal pseudotumors have been reported in the literature [5].

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The presence of a slowly enlarging mass in the limb or pelvis of a patient with hemophilia should rise suspicion of a possible pseudotumor, despite there have been rare reports of malignant tumors mimicking pseudotumors [6, 7].

Most pseudotumors are seen in adults and occur near the large bones of the proximal skeleton. However, a number develop distal to the wrist and ankle in younger patients before skeletal maturity. If untreated, proximal pseudotumors will destroy soft tissues, erode bone, and produce vascular or neurological lesions. Pathologic fractures can be associated.

10.2 Pathogenesis

Pseudotumors result from repetitive bleeding resulting in an encapsulated mass of clotted blood and necrosed tissue. The pathogenesis of pseudotumors has been much discussed by many authors, most of whom agree that their formation differs according to the anatomical site [8, 9].

Proximal pseudotumors occur in the proximal skeleton, especially around femur and pelvis; they appear to start in the soft tissues, erode bone secondarily from outside, and develop slowly over many years. They occur in adults and do not respond to conservative treatment. Repeated and unresolved hemorrhages, mostly caused by indirect trauma to the muscles, which all have a large area of origin like iliacus, vastus lateralis, and soleus, are the likely mechanism for formation

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_10,

and development of these lesions. They present as a painless expanding mass which is firm, often multilocular, and not tender, but is adherent to the deep structures. Such pseudotumors frequently remain painless and asymptomatic until there is a pathological fracture. The radiographic picture is typical with a large soft-tissue mass and areas of adjacent bony destruction. Calcification within the mass is common.

Distal pseudotumors predominantly affect younger, skeletally immature patients (children and adolescents) and are generally the result of direct trauma. It is not unusual to see such tumors distal to the wrist and ankle, especially in the small cancellous bones as the calcaneus, talus, and metatarsals of the feet but seldom in the carpus or other locations. These distal lesions develop rapidly, are painful, and appear to be secondary to intraosseous hemorrhage.

10.3 Pathology

A pseudotumor consists on blood products in different evolution stages surrounded by a fibrous capsule that contains macrophages charged with hemosiderin (Fig. 10.1). Calcification and later ossification may be seen within its wall. On histological examination, hemophilic pseudotumors resemble hematomas with a dense fibrous capsule. The cyst wall is formed by collagenous connective tissue, and the cavity contains a variable amount of organized fibrous tissue, thick "toothpaste-like" debris and liquefied clots. Other features that have been observed within the cyst cavity include bone fragments, foci of hemosiderin-loaded histiocytes, vascular neoformation within the cyst wall, osteoid neoformation, giant multinucleated cells, and foreign body-type cells [10, 11].

10.4 Clinical Presentation and Diagnosis

Patients present with painless palpable masses or with painful crises due to episodic acute bleeding into the tumor. Most of the morbidity from

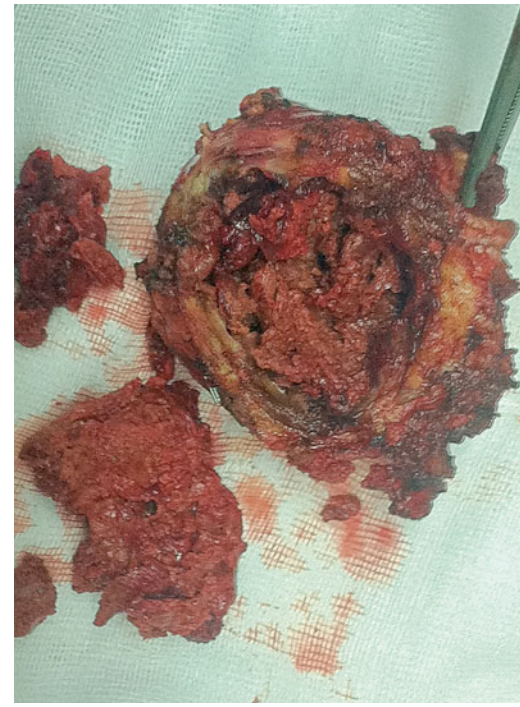

Fig. 10.1 Hemophilic pseudotumor opened after surgical resection

pseudotumors is due to their compressive effect on surrounding structures. Depending on the area involved, the symptoms include palpable masses, numbness, weakness, and neuralgia. Complications occur because progressive enlargement occurs, leading to compression of neighboring vital structures, destruction of soft tissues, and bone erosion, which may produce neurovascular complications. Ultimately there may be perforation through the skin or into adjacent organs, abscess and fistula formation, fatal hemorrhage, pathologic fractures due to bone destruction, and compartment syndromes due to vascular compromise and joint contractures [5].

In X-rays, lesions in proximity to long bones, there is a large soft-tissue mass with areas of adjacent bone destruction. The bone loss may be extensive, involving diaphysis and metaphysis and even destroying adjacent bones by crossing the joints. Periosteal elevation with new bone formation can be seen at the periphery of these lesions. Calcification and ossification within the soft-tissue mass are frequently noted [2, 12]. In

pelvic pseudotumors, the radiographic picture differs from those previously described in that the soft-tissue mass, and the extent of pelvic bone destruction, most of which occurs in the iliac wing, may be difficult to appreciate on plain X-ray films. Periosteal elevation and calcification within these lesions are much less common. An intravenous pyelogram should be performed if there is any concern about displacement of the ureters.

CT scans define the attenuation value of the tumor and thus help to differentiate it from other masses. It clearly delineates the size and extent of the tumor and compression of the adjacent skeleton, tissues, and organs. CT may prove useful in determining the origin of the pseudotumor and help follow its course. CT scans have been proven to be particularly efficient in the detection of daughter cysts, deep-seated cysts, and tumor extension into adjacent tissues, information that is useful in planning surgery [13].

Ultrasonography is ineffective for the detection of bony changes. It can be used after surgery to monitor for recurrence of pseudotumors in soft

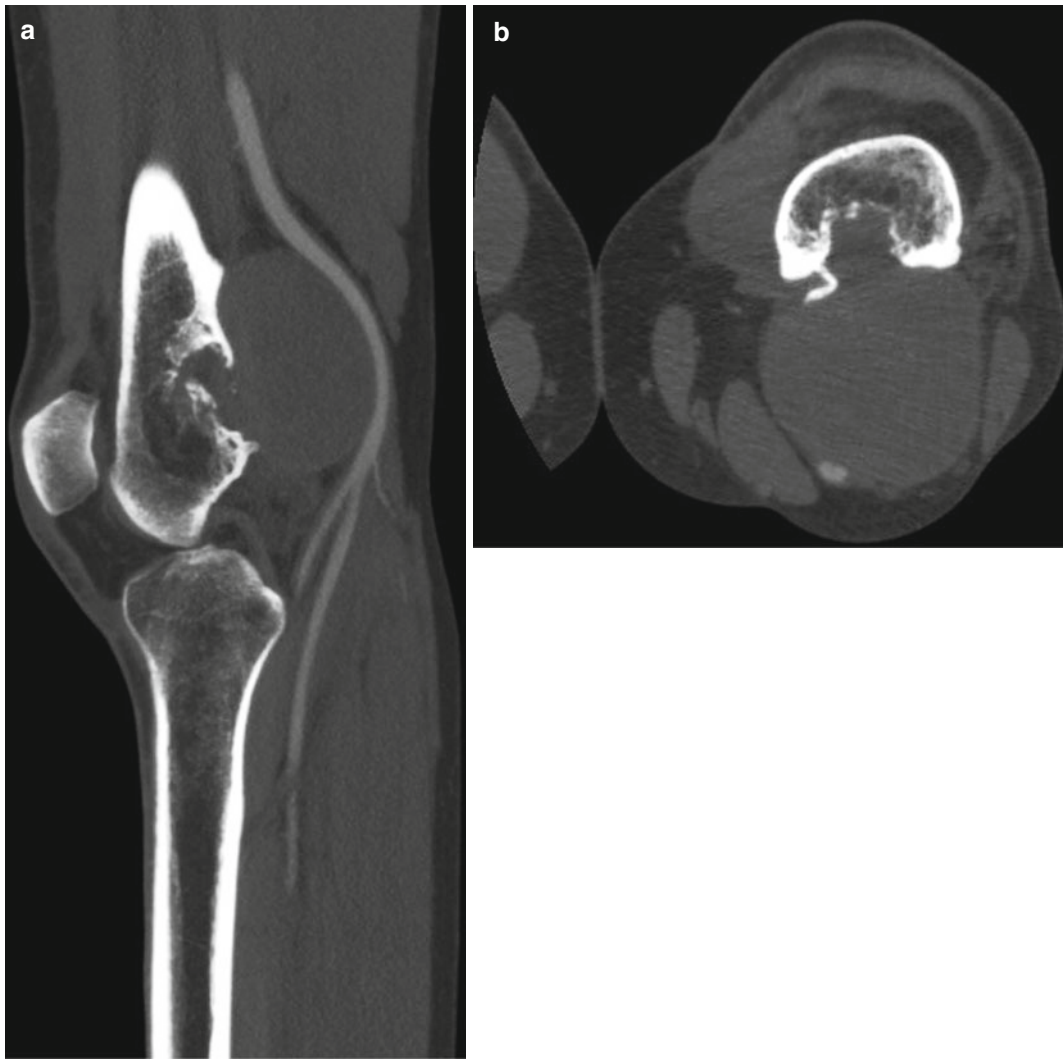

Fig. 10.2 CT of a hemophilic pseudotumor and its relationship with the popliteal artery: (**a**) sagittal view; (**b**) axial view

tissues. It has also been suggested as a low-cost alternative to monitor the progress of an existing lesion before obtaining a CT scan prior to repeated surgery [13].

MRI has been shown to be superior to other modalities for the imaging of soft tissues. MRI is sensitive for the detection of pseudotumors and can provide useful information for decisions regarding therapy and may be used to follow the response of a tumor to treatment. The appearance on MRI seems nonspecific with a similar appearance in tumors and abscesses, but invariably there are heterogeneous low and high signal intensity areas on both pulse sequences, reflecting the presence of blood products in various stages of evolution [14, 15].

CT and MRI scans are considerably more useful than plain X-rays and may be sufficient to evaluate displacement of the large vessels (Fig. 10.2). Imaging characteristics of pseudotumors are rather nonspecific, but given a history of hemophilia, radiologists must be aware of these to avoid misinterpretation.

10.5 Treatment

The management of the patient with a hemophilic pseudotumor is complex and carries a high rate of potential complications. It is important that they are diagnosed early, and prevention of muscular hematomas is key to reducing their incidence. Muscle hematomas should be avoided by primary prophylaxis, and if a muscle hematoma does develop, it must be treated hematologically on a long-term basis until total shrinkage and disappearance of the hematoma have occurred [16].

Hemophilic pseudotumor are uncommon; therefore, there is no consensus about specific management. There are different treatment options (surgical removal and exeresis, and filling of the dead cavity, percutaneous management, embolization, radiation), and it would be necessary to individualize therapy. With the increasing availability of factor replacement, surgical removal is feasible.

Preoperative biopsy or aspiration of the fluid within the cysts for either diagnostic or therapeutic purposes is contraindicated. The cystic contents are too thick to permit successful aspiration, and there is a high risk of relapse, infection, or the development of a persistent fistula [10].

Conservative treatment includes long-term factor replacement and immobilization of the affected area. Distal pseudotumors in children respond well to conservative approach. However, it fails to prevent progression of the lesion especially in proximal lesions, and recurrence and progression is the rule [6].

10.5.1 Surgical Removal

Surgical removal is the treatment of choice when it can be carried out in major hemophilia centers and careful preoperative planning can be done, because these procedures are fraught with difficulty and carry a high complication rate. Surgery is the most effective treatment and should be performed upon diagnosis when the pseudotumor is still small and relatively easily resected. Lesions in proximity to the long bones and lesions of the pelvis should be managed in different ways, and in fact, the surgical approach to these lesions must be individualized.

When the lesion is in the proximity of long bones, the aim should be complete resection of the lesion, stabilization and bone grafting if required, hemostasis, and closure of the dead space. Implantation of a tumoral prosthesis for reconstruction of massive juxta-articular bone lesions can be necessary; although the authors have no experience with this type of reconstruction in hemophilic pseudotumors, it is routinely used for reconstruction after resection of bone sarcomas, and primary arthroplasty in hemophilic patients is also a common procedure in our hospital. The incision has to be planned to allow access to the neurovascular structures, removal of the lesion, and fixation of bone if necessary. Neurovascular structures should be identified and retracted prior to remove the blood cyst (Fig. 10.3). It usually is within a muscle mass and during dissection tries to stay on the fibrous capsule and then as much muscle as possible should be preserved. The portion of muscle wall that is directly adjacent to the

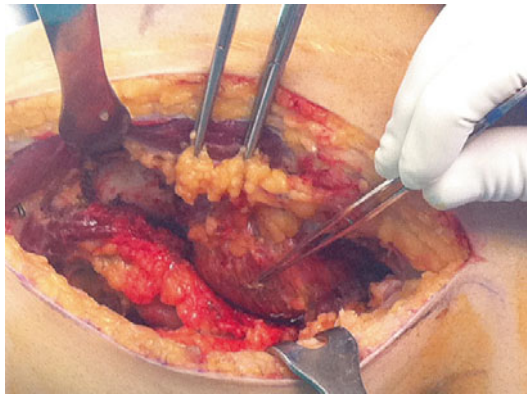

Fig. 10.3 Intraoperative view of the pseudotumor seen in Fig. 10.2

bone can be removed easily with cautery dissection and curettes. Bleeding from the bone or other surfaces can be controlled during surgery by the use of fibrin glue. Bone fixation is an important part of the procedure when necessary; intramedullary nailing has been most often used to stabilize diaphyseal or proximal femur fractures, but when the lesions are around the knee, fixation with periarticular plates can be more useful. Reconstruction of the bone defect after removing the pseudotumor can be done with bone graft, bone substitutes, or bone cement (Fig. 10.4), especially in metaphyseal or epiphyseal defects that involve mechanical risk. At this point, meticulous hemostasis should be obtained. Coverage of the remaining bone should then be addressed, using a muscle flap if necessary. A suction drain is always used and a bulky pressure dressing applied. The use of plaster and the weight-bearing status

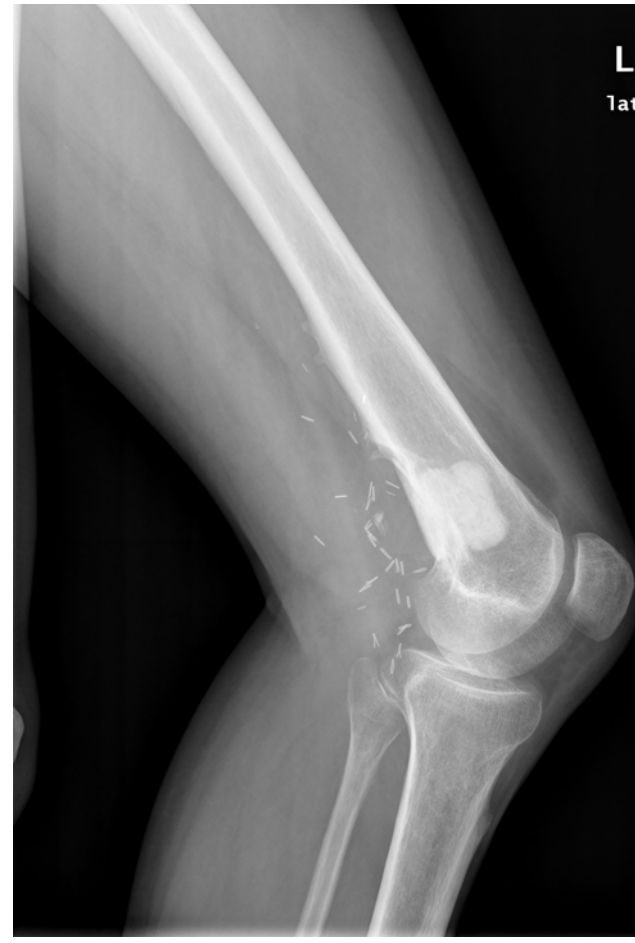

Fig. 10.4 Postoperative radiograph. The pseudotumor was removed and the bone defect filled with bone cement

must be calculated for the individual patient, depending upon the lesion itself and the extent of arthropathy in other joints. Nonunion of pathological fractures has not been a problem, because large denuded bone surfaces result in abundant new bone formation.

Pseudotumors of the pelvis develop following hemorrhage into either the iliacus or iliopsoas muscles. It is wiser to perform this procedure in connection with general surgeon. The surgical approach to the pelvic blood cyst is different from that for the extremities. Before starting the procedure, a ureteral catheter is placed so that the ureter can be more easily identified during surgery. The patient is placed on his or her back with the affected side of the pelvis on two sandbags with the lower limb draped free. A flank incision, starting at the proximal aspect of the mass and approximately 3 cm above the iliac crest is made, extending distally to the inguinal ligament and then continuing distally in order to expose the femoral vessels and nerve which should be identified. The flank muscles are then divided and the cysts can be identified. If possible, the dissection is kept within the retroperitoneum. If complete excision of the cyst is impossible, the cyst can be opened and evacuated removing sections of the cyst. Manipulation of vessels, the ureter and the femoral nerve must be very careful to avoid iatrogenic injuries of such structures. Fibrin glue should be used as an adjuvant to control bleeding. One can leave a small cuff of capsule attached to these important structures and do not damage them. Massive pseudotumors in the pelvis can affect the hip joint; these challenging cases can be impossible to successfully treat or reconstruct. Many methods have been employed to eliminate the dead space, including the use of omentum, muscles, dexon mash, and bone grafting. Pelvic pseudotumors distort natural anatomy causing major displacements of bowels, ureters, nerves, and blood vessels thus increasing the likelihood of injury during surgery. It is our belief that pseudotumors should be excised in order to prevent them from reaching inoperable dimensions. The management of patients with massive pseudotumors, where the aim of treatment is improvement of the quality of life and not total eradication of the tumour, requires that the patient and their family understand the treatment goals. It is essential that psychological counselling be available before, during, and after the surgical procedure. One of the major problems with surgery in patients with massive pseudotumors is that one knows the starting point but one is never sure of where and when the procedure will end. The decision to operate should not be taken lightly, for the complications include fistula formation, regrowth of the pseudotumor, sepsis, bleeding, and death [17, 18].

There is a significant amount of hemorrhage during and following these procedures. Replacement therapy and transfusion requirements should be carefully considered by the hemophilia team before undertaking surgery.

10.5.2 Radiation

Although surgical excision of hemophilic pseudotumors is currently considered as the preferred management modality, there are instances in the literature that because of certain impediments surgery could not be easily performed and radiotherapy may be beneficial. The exact mechanism of action of radiotherapy is unknown; however, it presumably acts by causing injury to blood vessels and fibrosis. Despite the limited data some conclusions can be pointed out. There was a failure rate of around 25 %, most of which are related to adjunctive treatment modalities implemented, location of pseudotumor, and the size of pseudotumor [19]. Most of treatment failures occurred in patients with proximally occurring masses within pelvis and femur. Distal pseudotumors and the ones which were located in upper limbs or skull generally were more amenable to radiotherapy. This treatment modality may be beneficial for

unresectable lesions. Irradiation prior to surgery is not, in Heim's opinion [17], recommended, as the ensuing fibrosis will make surgery more difficult. Once the pseudotumor has been excised, focal irradiation to any remaining capsule may be beneficial.

10.5.3 Embolization

Pseudotumors are avascular internally but have a very rich blood supply in the capsule. This is most probably the reason for repeated hemorrhages inside the capsule, which result in the expansion of the mass. The rich vascular supply of the capsule is the cause of excessive bleeding during and after the surgery. Regarding the role of arterial embolization in hemophilic pseudotumor management, it should be considered in lesions of large size, especially in pseudotumors of pelvic region, as it may effectively reduce its size and decrease the risk of bleeding complications during surgery. Nevertheless, in view of its temporary effect, embolization had better be performed as a preparatory procedure, at best about 2 weeks prior to surgery. This time lapse will allow for mass shrinkage but is insufficient for vessel restoration [19].

10.5.4 Percutaneous Management

Curettage and filling with fibrin seal and cancellous bone graft via the percutaneous insertion of a trocar into the cyst has been recommended by Caviglia et al. [20]. There may be some value in this treatment modality in small lesions. In advanced or potentially inoperable pseudotumors, there is a role for percutaneous aspiration, but evacuation of the contents of the pseudotumor may be difficult and there is a risk of infection and permanent fistula. In soft-tissue pseudotumors, evacuation and filling of the cavity are carried out assisted by ultrasound, while in pseudotumors affecting bone, this is performed with an image intensifier or CT scan and video assistance. If the cavity content is liquid, it is easy to aspirate, but solid contents cannot be evacuated by aspiration and will need to be washed out and removed with curettes. Cavities of <3 cm may be filled with fibrin seal; larger cavities should be filled with a lyophilized bone graft or a bone substitute. When the pseudotumor is in the bone, the location, size, and degree of its cortical compromise will be evaluated to confirm the true loss of the bone stock. When the pseudotumor is diaphyseal or diaphy-metaphyseal, it generally consists of a single cavity. In contrast, with a pseudotumor that is epiphyseal or epiphy-metaphyseal (in cancellous bone), the cavities are multiple. Lack of aspiration of one cavity may lead to only partial cure of the lesion. It is very important to clarify the bone damage to prepare bone reconstruction or mechanical support if needed.

Conclusions

A pseudotumor is basically an encapsulated hematoma; it has become rarer over the years with better treatment modalities for bleeding disorders like factor replacement. Its prevention is paramount; this goal can be achieved by primary prophylaxis to avoid muscle hematomas and by adequate and long-term hematological treatment of muscle hematomas in case they appear. There are a number of therapeutic alternatives for this dangerous condition: surgical removal, percutaneous management, exeresis and filling of the dead cavity, irradiation, and embolization. The management of the patient with a hemophilic pseudotumor is complex and with a high rate of potential complications. Surgical excision is the treatment of choice but should only be carried out in major hemophilia centers by a multidisciplinary surgical team. The main postoperative complications are death, infection, fistulization, and pathological fractures (requiring even amputation of the affected limb).

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Orthopedic Surgery in Hemophilia: Is Thromboprophylaxis Necessary?

11

E. Carlos Rodríguez-Merchán and
Hortensia De la Corte-García

11.1 Introduction

In the white population of the USA, the incidence of venous thromboembolism (VTE) is between 71 and 117 cases per hundred thousand inhabitants [1]. It is estimated that each year about 1 million people suffer VTE. The annual cost of VTE is approximately 1.5 billion dollars (US dollars).

At present, most authors use some form of thromboprophylaxis when performing orthopedic surgery; the goal is to reduce the risk of VTE [1–7]. There are basically two types of preventive measures for VTE: pharmacological and mechanical.

The most common pharmacological thromboprophylaxis is performed with low-molecular-weight heparin (LMWH) subcutaneously; however, oral anticoagulants (fondaparinux, dabigatran, apixaban, rivaroxaban) are now increasingly being used. On the other hand, mechanical thromboprophylaxis includes progressive compression stockings, intermittent pneumatic compression devices, and foot pumps. In orthopedic surgery on non-hemophilia patients, the authors believe that the combination of pharmacological and mechanical measures is the best option [1–7].

However, in hemophilia patients undergoing orthopedic surgery, there is still much controversy over whether or not to perform some kind of thromboprophylaxis. The aim of this chapter is to clarify whether in hemophilia patients undergoing orthopedic surgery, thromboprophylaxis should be performed or not. In pursuing this objective, we have reviewed the literature with the most evidence on non-hemophilia patients and the existing publications on the same subject in hemophilia patients. Finally, we will analyze our 38 years of experience in the role of thromboprophylaxis in orthopedic surgery for hemophilia patients.

11.2 Search Strategy

We searched the literature from January 2000 to December 2013 for articles published in English in PubMed (MEDLINE), which were related to thromboprophylaxis in hemophilia patients undergoing orthopedic surgery. Keywords used were hemophilia, thromboprophylaxis, and orthopedic surgery. We found seven articles with a high degree of scientific evidence regarding thromboprophylaxis in orthopedic surgery in the general population. We also found eight articles related to the same subject in hemophilia patients.

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_11,

11.3 General Concepts

The evidence-based medicine studies have shown that subcutaneous injections of LMWH are currently the best thromboprophylaxis in patients undergoing orthopedic surgery [1]. LMWH is effective, safe, and relatively inexpensive.

It makes no difference whether you start the thromboprophylaxis with LMWH 12 h before orthopedic surgery or 12–24 h after surgery, as it has not been demonstrated that either of the options is better than the other. Thromboprophylaxis with LMWH should last 30–42 days (4–6 weeks), and it effectively reduces the frequency of postoperative symptomatic VTE, especially in patients undergoing total knee replacements (TKR) (Fig. 11.1) and total hip replacements (THR) (Fig. 11.2). Mechanical thromboprophylaxis measures (graduated compression stockings, intermittent pneumatic compression devices, and foot pumps) also reduce the risk of VTE, and they are useful adjuvant methods combined with pharmacological thromboprophylaxis [1].

For patients undergoing orthopedic surgery, the American College of Chest Physicians (ACCP) [2] has indicated that it is best not to use thromboprophylaxis for at least 10–14 days. This thromboprophylaxis can be performed with LMWH, with oral anticoagulants such as fondaparinux, dabigatran, apixaban, and rivaroxaban (THR or TKR but not in hip fractures) with low doses of unfractionated heparin, with adjusted doses of vitamin K antagonists, with aspirin, or with intermittent pneumatic compression device.

The ACCP's preference is a combination of pharmacological thromboprophylaxis with LMWH for up to 35 days and an intermittent pneumatic compression device during hospitalization. In patients at high risk of bleeding, the ACCP recommends an intermittent pneumatic compression device or the absence of thromboprophylaxis. In patients undergoing arthroscopic surgery with no history of VTE, the ACCP advises against thromboprophylaxis. The aforementioned recommendations have been endorsed in other studies with a high level of evidence [3–7].

11.4 Thromboprophylaxis in Hemophilia Patients Undergoing Orthopedic Surgery

In 2000, Pruthi et al. [8] presented a patient with moderate hemophilia B (treated with factor IX concentrate) who suffered VTE in the operated leg after a THR for a hip fracture. It was later detected that the patient was a heterozygous carrier of the factor V Leiden mutation. His conclusion was that it could be useful to perform preoperative screening on those hemophilia patients who had previous history of VTE. That same year, Manucci [9] recommended that all thrombophilic patients should carry out short-term thromboprophylaxis with LMWH whenever they were exposed to significant risks (surgery, prolonged immobilization).

In 2004, Dargaud et al. [10] noted that, given the absence at that time of recommendations on thromboprophylaxis in people with hemophilia, this prophylaxis should not be routinely performed. However, they also noted that hemophilia does not fully protect against VTE. Therefore, they recommended performing thromboprophylaxis in specific cases in which there are clear risk factors.

In 2006, Butcher and Pasi presented a patient with hemophilia A, undergoing major pelvic surgery [11], who had several risk factors and ultimately died of a pulmonary embolism. Their conclusion was similar to that of Dargaud et al. [10].

In 2012, Uprichard et al. [12] analyzed a series of 13 TKRs in 11 patients with hemophilia B, who received mechanical thromboprophylaxis and 1 also received pharmacological thromboprophylaxis. No patients suffered VTE.

In 2012, Krekeler et al. [13] analyzed 85 patients (105 interventions, 90 with major orthopedic surgery, and 15 with minor surgery) without finding any cases of postoperative VTE despite not performing any kind of thromboprophylaxis. In 2012, Ozelo [14] reached the same conclusions as Butcher and Pasi [11] and Dargaud et al. [12]. In 2013, Berntorp [15] noted that in elderly hemophilia patients and in patients with von Willebrand disease, it will be necessary to assess

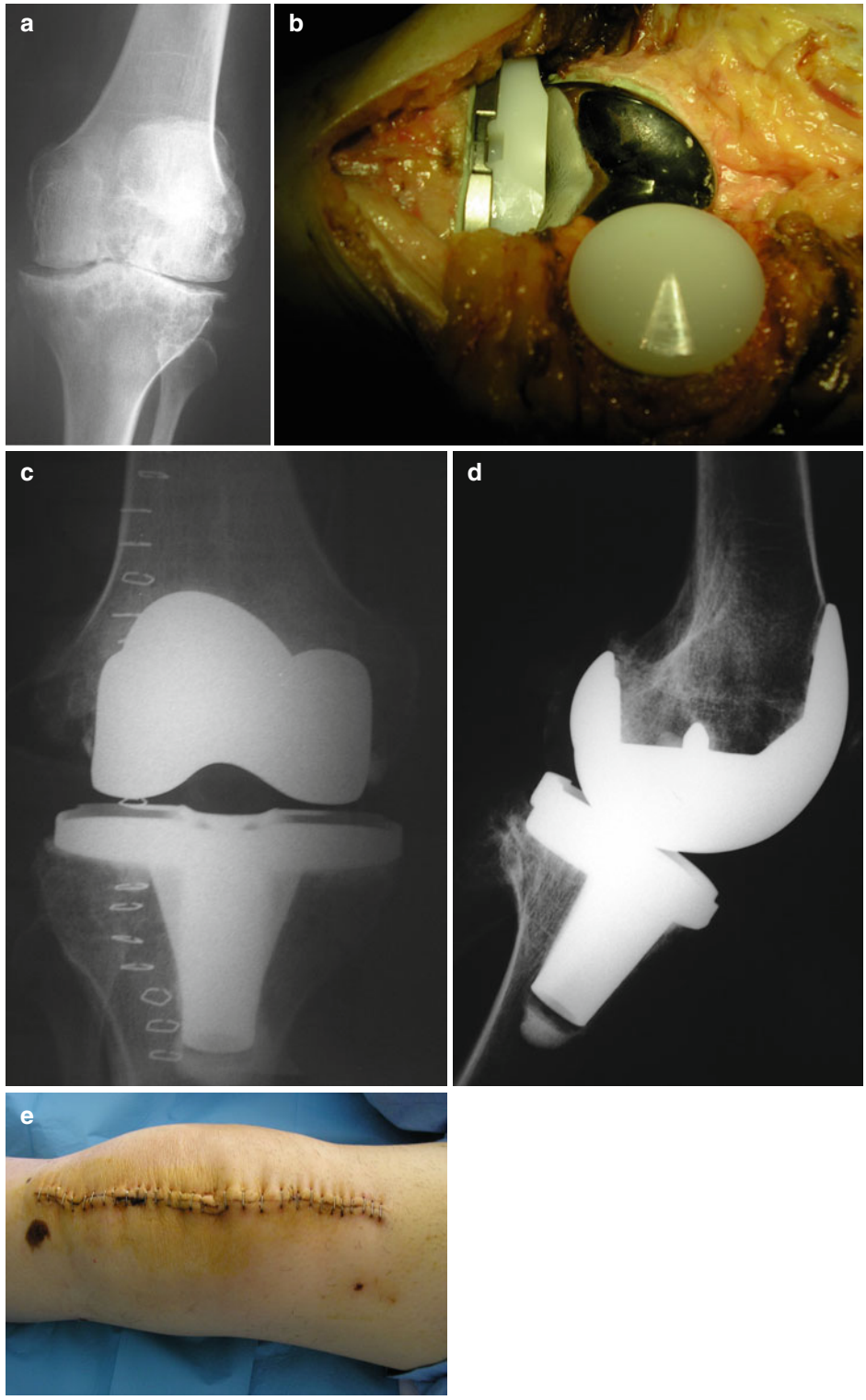

Fig. 11.1 Total knee replacement (TKR) in a patient with hemophilia. Pharmacological thromboprophylaxis was not used: anteroposterior preoperative radiograph (**a**). Intraoperative view (**b**). Anteroposterior postoperative radiograph (**c**). Lateral postoperative view (**d**). Clinical view after surgery (**e**)

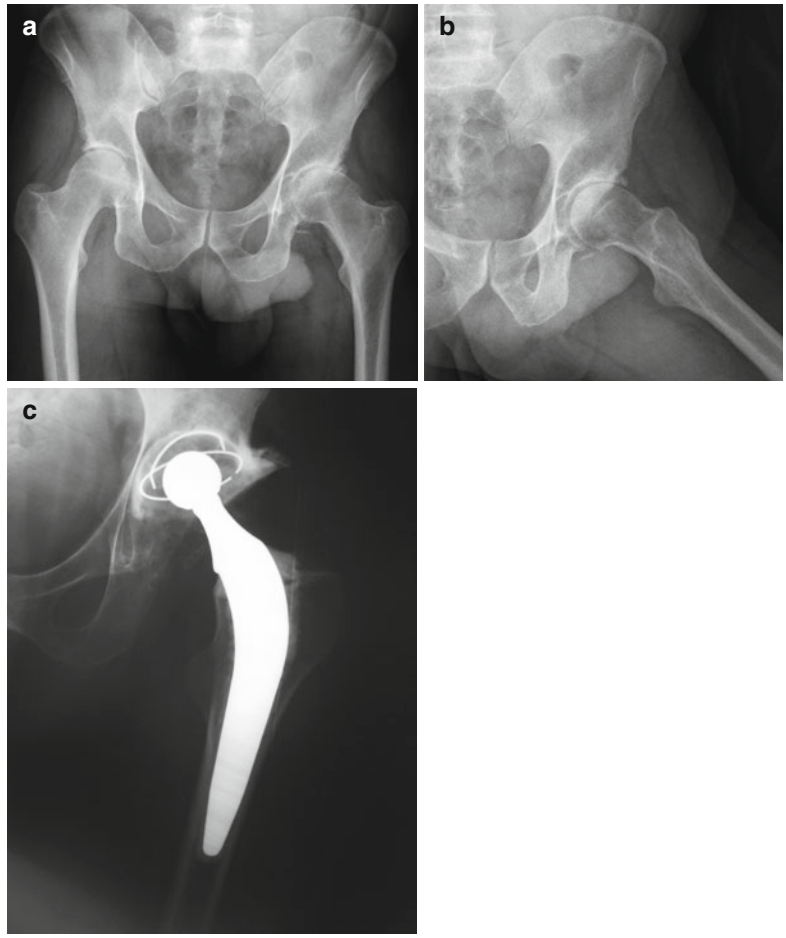

Fig. 11.2 Total hip replacement (THR) in a hemophilia patient performed without using pharmacological thromboprophylaxis. Anteroposterior preoperative radiograph (**a**). Lateral preoperative view (**b**). Postoperative radiograph (**c**)

the risk-benefit balance of thromboprophylaxis when they undergo major orthopedic surgery.

According to Ozelo for the majority of the patients, the use of gradated compression stockings and early mobilization can be sufficient to prevent venous thromboembolism [14]. The use of anticoagulant prophylaxis should be considered just for patients with relevant additional risk factor for thrombosis. However, for hemophilia patients with inhibitor, pharmacologic thromboprophylaxis is not recommended. For patients with von Willebrand disease receiving factor concentrates replacement therapy undergoing surgical procedures, the FVIII plasma levels should be monitored and thromboprophylaxis should be considered if any other thrombosis risk factor is present. It is important for the future to establish risk assessment tools that can help to determine the most effective and safe practice to prevent venous thrombosis in patients with hemophilia and other bleeding disorders who undergo surgical procedures.

11.5 Authors' Experience

In a period of 40 years, the corresponding author has performed 465 orthopedic surgical procedures on 403 patients with hemophilia (100 TKR, 23 THR, and a further 274 major surgeries), plus 68 minor orthopedic surgical procedures (arthroscopies and other). Thromboprophylaxis measures

were never used (neither pharmacological nor mechanical) except rapid postoperative mobilization of patients. This comprised getting the patients out of bed the day after surgery and performing active and passive mobilization of the limbs. We must point out that in hemophilia, we have always used general anesthesia, which is a known risk factor for VTE. Fortunately, we have never clinically detected deep vein thrombosis in any of our patients.

Conclusions

Based on the review of the literature from the year 2000 to June 2013 and our own experience of 40 years performing orthopedic surgical procedures on hemophilia patients, we can state that thromboembolic complications in hemophilia after this surgery are extremely rare. Therefore, we cannot recommend widespread thromboprophylaxis on hemophilia patients undergoing orthopedic surgery. In fact we have never performed it (although we have always practiced rapid postoperative mobilization of patients after orthopedic surgery). This contrasts sharply with non-hemophilia patients, for whom all authors agree that mixed pharmacological and mechanical thromboprophylaxis is highly recommended. If we detect a clear risk factor for thromboembolism in a hemophilia patient, personally, we would recommend performing the same type of thromboprophylaxis as on non-hemophilia patients. Such risk factors are orthopedic surgery, general anesthesia, increased age, obesity, previous thromboembolism, varicose veins, factor V (Leiden) mutation, malignancy (cancer), and the oral contraceptive pill.

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Rehabilitation of Joint Surgery in Hemophiliacs

12

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12.1 Introduction

Hemophiliac arthropathy is a frequent cause of pain and disability. The increased life expectancy in the hemophilia population has made surgery a good therapeutic option for relieving pain and reducing the dependence of a large number of patients suffering from osteoarticular pathology that is secondary to the repeated hemarthroses caused by clotting factor deficiency. The development of new hematological treatments together with progress in surgical and anesthetic techniques has greatly contributed to this situation. Another factor that has contributed to improving these patients' quality of life has been the advances made in rehabilitation treatments throughout the pre- and postsurgical process, which make it possible to maximize functional outcomes [1].

A discussion of rehabilitation in joint surgery on patients with hemophilia may be as extensive as a discussion of the surgical options and techniques. This wide range of surgical options makes it very difficult to discuss the rehabilitation aspect exhaustively. In this chapter we will therefore review the general bases of rehabilitative medicine, focusing on common factors in joint surgeries on patients with hemophilia in terms of therapeutic goals, treatment techniques, levels of disability, and special characteristics. The ultimate goal of rehabilitation will always be to return the patient to the highest possible level of functional independence.

12.2 General Concepts

In many patients with hemophilia, joint disease appears at a much younger age than what is common in the general population [2]. The most significant chronic musculoskeletal symptoms in patients with hemophilia continue to be synovitis and arthropathy, which often affect the elbow, the knee, and ankle joints [3].

The main reasons for operating on patients with hemophilia are disabling joint pain, changes to joint function and loss of independence when carrying out everyday activities, which cannot be alleviated by other therapeutic methods. In this case, the orthopedic surgeon will decide which surgical technique is most appropriate for each patient.

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_12,

There are several operations that may relieve the symptoms of hemophiliac arthropathy, including joint debridement (by arthroscopy or open surgery), osteotomy, arthroplasty, and arthrodesis [3]. It must be borne in mind that orthopedic surgery in patients with hemophilia requires much more preparation and greater precautions than surgery on patients who do not have hemophilia [4]. Luckily, the availability of clotting factor concentrates makes it possible to perform major surgery, including several procedures in the same operation [2, 3, 5, 6].

Currently it is also possible to carry out the abovementioned surgical techniques on patients with circulating inhibitors, although in their cases, special hematological, surgical, and rehabilitation considerations will have to be taken into account [7, 8].

For rehabilitation to be successful within a postsurgery context, coordination between health professionals is essential. It is of paramount importance that the details of the surgery are taken into account when planning the best rehabilitation program. These details are basically: the approach route, the type of injury found, the exact procedure performed, and any incidents arising during the operation.

Rehabilitation must create a protected environment that facilitates tissue repair while steady progress is made towards recovering more function, in terms of pain control, improvements to muscle strength and joint mobility, and reeducating the gait and in other daily activities. There is a comprehensive arsenal of treatment techniques that can be used to achieve these goals, which can be classified on the basis of their underlying physical principles. It is advisable to use replacement clotting factor while therapy sessions are ongoing, in order to minimize the risk of hemorrhages [2].

12.3 Patient Assessment

It is essential that hemophiliac patients with osteoarticular pathology, especially those for whom surgery is an option, be evaluated from the point of view of rehabilitation. The assessment must be repeated from a broad clinical and functional perspective on a regular basis during the pre- and postsurgical process. The patient's degree of disability in the different areas of his or her life must be considered, taking into account each patient's individual characteristics and social environment. For patients with serious medical illnesses or a general loss of function, the suitability of surgery must be very carefully assessed.

The preoperative assessment should include a full clinical history, detailed physical examination, and additional tests (X-rays, ultrasonography, magnetic resonance imaging-MRI, computed tomography-CT) that will help us determine the patient's status in terms of function. It must be borne in mind that the state of patients with hemophilia who undergo joint surgery has usually deteriorated and often involves polyarticular problems, muscle hypotrophy, joint deformities, compensatory kyphoscoliosis, and/or length discrepancy in limbs, and these factors must also be carefully evaluated [2, 9] (Fig. 12.1). During the evaluation, the parameters described in the Table 12.1 should be collected.

It is advisable to use rating scales to unify criteria, measure the effectiveness of the operation carried out, and monitor the patient's clinical progress throughout the various stages of treatment. For adults, Gilbert is the most widely used scale [1–3]. On the other hand, in order to be able to objectively quantify these patients' functional level, it is essential to use assessment tools that take into account the patient's psychological recovery and their social integration, such as the functional rating scales. Although no specific scales are available for hemophilia patients, the generic ones most commonly used in daily clinical practice are: FIM (*Functional Independence Measure*), Barthel index, and HAQ (*Health Assessment Questionnaire*) [1–3].

12.4 Objectives of Rehabilitation

Once the patient's clinical and functional status has been evaluated through clinical and functional assessments and image tests, the course of action can be determined. There is no doubt of the effectiveness of rehabilitation for hemophiliac patients undergoing joint surgery, and there is virtually unanimous agreement on the benefit of applying it throughout the process.

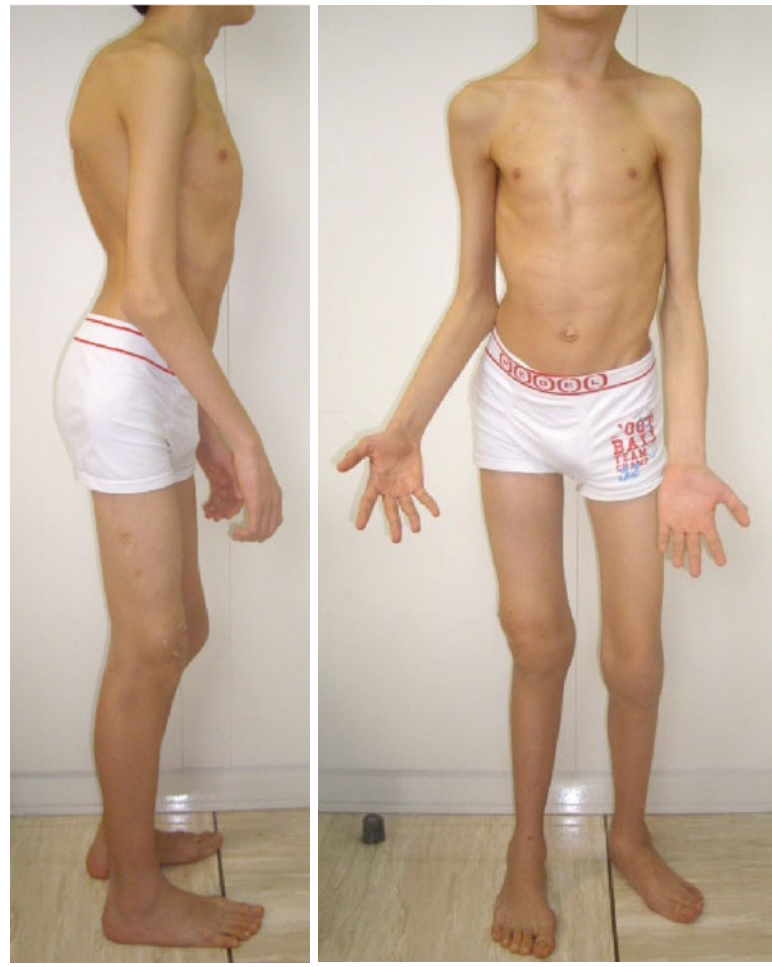

Fig. 12.1 Sixteen-year-old hemophilia patient with musculoskeletal impairment in several areas. Note the kyphoscoliosis, pelvic obliquity, arthropathy in both elbows and the left knee with reduced extension in these joints, and muscle hypotrophy. He also has arthropathy of the left ankle with flat foot and valgus deformity and acute hemarthrosis in the right knee with genu valgus deformity

Table 12.1 Overall assessment of the patient with hemophilia

Hemodynamic status of the patient
Static postural
Pain focused on bony structures or soft parts
Joint mobility ranges
Trophism and muscle strength
Deformities or pathologies associated in the kinetic chain
Osteoarticular problems in other limbs or vertebral column
Neurovascular status of member
Bimanual skill and walking if possible
Cardiorespiratory impairment, concomitant pathology, age, previous immobility, cognitive status, sequelae of previous injuries, medications, etc.

The ultimate objectives are to: prevent complications, improve the functionality of the limb operated on, and prepare the patient for carrying out their everyday activities independently. This applies, in the case of surgery on joints in the upper limbs, to improving the manual dexterity and skill necessary for everyday activities, and, in the case of lower limb surgeries, to gait reeducation and training in walking up and down stairs. These overall objectives can be broken down into more specific objectives, which are shown in the Table 12.2.

It is essential to establish realistic therapeutic goals and determine the program and treatment techniques that will be used to achieve these goals. The therapeutic program should be individualized, adapted to the situation of each patient [10].

Ideally, the rehabilitation treatment should be started early, even if the segment involved needs to be immobilized, as this does not have to mean that the patient is completely immobilized.

Table 12.2 Objectives of rehabilitation in hemophiliacs undergoing joint surgery

Relieve pain
Regain range of joint motion
Improve muscle strength and trophism
Regaining proprioception and muscle balance
Prevent muscle atrophy, deformities, demineralization, and other sequelae
Improve functional capabilities
Maintain an appropriate pattern of movement when walking
Improve quality of life

The success in treating these patients will also depend on the work done by a multidisciplinary team of professionals collaborating on a common goal (orthopedic surgeon, hematologist, rehabilitation physician, nurses, physiotherapists, occupational therapists, orthopedic technicians).

12.4.1 Preoperative Rehabilitation

The first preoperative visit should take place 4–6 weeks prior to the operation. In it, the doctor responsible for the rehabilitation treatment must evaluate the patient and inform him or her on the postoperative process and the need to be receiving hematological treatment while the physical treatment is ongoing [11]. Clear information allows reducing patient's anxiety, analgesic use and the hospital stay after surgery. It is also important to determine how motivated the patient is to participate in a postoperative rehabilitation program; those patients who are not motivated enough may not be accepted [2, 12].

A physical and functional assessment of the patient will identify any mobility problems and specific needs to assist in moving about after the operation. As a result, it will be possible to order any equipment that may be required during the postoperative period to assist with adaptation, in order to ensure that it is delivered to the patient on time. This type of equipment may include wheelchair, crutches, orthotics, footwear, technical aids, or adaptations for home [2].

Preoperative physiotherapy programs are not indicated in all cases, because for some conditions they have not been shown to improve the results over the long term [2, 12]. It must be borne in mind that if a patient with hemophilia is to undergo surgery on a joint, it is because other more conservative therapeutic interventions, including rehabilitation, have previously been tried and failed to solve the problem.

Patients should always be instructed to do the rehabilitation exercises learned in prior therapeutic programs daily at home [2].

If it is decided that new preoperative rehabilitation treatment should be prescribed, the objective will be the same. These programs may include respiratory therapy techniques, postural standards, spinal hygiene, global kinesitherapy of all four limbs, balance techniques, learning transfers, and use of external aids. Table 12.3 reflects the contribution of medical rehabilitation during the preoperative period.

Table 12.3 Contribution of rehabilitation physician in the presurgical phase of the hemophiliac patient

Explain the postoperative process
Inform as to realistic expectations about the results to be expected in the long term
Determine the patients' degree of motivation to participate in a rehabilitation program
Perform a physical and functional assessment of the patient before the operation
Identify possible mobility difficulties that could affect postoperative gait
Prescribe the equipment that may be required for adaptation after the operation (crutches, orthosis, footwear, technical aids,..)
Consider the patient's social environment, family support and the need for adaptations to the home
Advise that the exercises learned in previous therapeutic programs must be followed daily at home
Prescribe additional sessions of physiotherapy/occupational therapy to work on specific techniques, make transfers and use external aids under the supervision of a therapist
Bring the patient to the best possible condition in general and functional terms in preparation for the operation

12.4.2 Postoperative Rehabilitation

Postoperative rehabilitation programs are fundamental to optimizing the results of surgery and are

nowadays considered essential to ensure proper improvement after surgery. That is to say, there are no doubts as to the benefits of such programs. It is important to note that surgery can improve hemarthrosis and pain, but not all the associated problems that have evolved over the years. In this respect, arthroscopy makes it possible to perform a synovectomy and perform chondral debridement but will not solve the muscle atrophy or the reduced joint mobility, the instability, or loss of proprioception. The osteotomies and the arthroplasties usually improve mobility, joint stability, and deformity correction [5].

The patient should be reassessed as soon as possible after surgery, in order to ascertain their clinical and physical status and to be able to establish goals for rehabilitation. The orthopedic surgeon can describe the assessment made during surgery, any problems encountered, and the plan to have the patient kept immobile or non-weight-bearing, if necessary, and so must be contacted to obtain all this information. Additionally, the hematologists must be in touch, since good postoperative hemostatic coverage is vital during rehabilitation. All members of the team should have experience in handling people with hemophilia [13].

If there were no complications with the operation, the therapeutic rehabilitation program should begin early, during the period of hospitalization, and then continue as an outpatient program.

During the first 24–48 h after surgery it is paramount to control hemostasis and pain; also to follow some postural recommendations that will allow the patient to maintain the operated limb in good alignment and in good articular, muscular, vascular and neurological state.

Immediately after this period, a more demanding therapeutic program can begin, in which an experienced therapist will apply the physiotherapy techniques appropriate to each case. One or two treatment sessions per day are usually recommended for a period of about 6 weeks, depending on the clinical evolution [2, 14]. Rehabilitation of a patient with hemophilia has some specific characteristics that must be borne in mind and are described in Table 12.4. To reduce the risk of infection through the surgical wound, the highest possible hygiene standards must be maintained. Pain medication will be used throughout the whole time the patient is undergoing rehabilitation treatment. Hemostatic coverage is essential; if clotting factor infusion is not continuous, physiotherapy and occupational therapy should be scheduled on the basis of the timetable for clotting factor infusion [2]. According to the latest published guides: during the first three days after the operation, patients must maintain clotting factor concentrations of 60–80 IU/dl (in hemophilia A) and 40–60 IU/dl (in hemophilia B); for the fourth to sixth days, these levels should be 40–60 IU/dl (in hemophilia A) and 30–50 IU/dl (in hemophilia B); during the second week, the recommended level is 30–50 IU/dl (in hemophilia A) and 20–40 IU/dl (in hemophilia B) [13], in order to maintain concentrations of at least 40 %, and patients may begin to receive one infusion per day. During the third and fourth weeks after the operation, patients receive 20–40 IU/kg/day, depending on the clinical condition of the joint that has been operated [2]. Therefore, if there is any increase in inflammation or pain during the rehabilitation period, it is recommended that an immediate treatment of a full dose of clotting factor concentrate is administered for several days, until symptoms disappear. Before removing the sutures, factor concentrate should be administered if it has not yet been administered on a regular basis [2]. The general

Table 12.4 Specific aspects of the postoperative rehabilitation program in patients with hemophilia

Maximize hygiene standards and the treatment during assessment
Maintain proper hemostatic coverage during the rehabilitation period, to reduce the risk of bleeding
Control pain with the use of multimodal analgesia and avoiding NSAIDs
Schedule physiotherapy and occupational therapy sessions to coincide with clotting factor infusion
Close monitoring of possible complications, which usually require hematological and rehabilitation therapy to be adjusted immediately
In those joints for which there is a significant risk of developing a flexion contracture, a hinged orthosis is very useful
To achieve maximum functional recovery, any preexisting musculoskeletal problems must be considered and treated

Table 12.5 The general guidelines for a rehabilitation program after joint surgery without complications in patients with hemophilia

1–3°day	Postural control. Full joint extension. Passive or assisted mobilization of 0–40°. Start isometric muscular work[a]. Sedestation. CPM can be used for arthroplasties
4–7°day	Increase the movement of the joint (progressing at a rate of 5–10°per day). Isotonic muscle work[a]. Bed-chair transfers. Progressive increase in bipedal standing and walking with partial weight-bearing[b]
2–4°weeks	Release of soft tissues. Progress in ROM, muscle strength[a], and joint balance. Reeducation of the gait pattern and recovery of functional skills
>4°week	Walking around obstacles, ramp, stairs. Reeducation in everyday activities (personal hygiene, clothing.)

Progression in the treatment will depend on postoperative time and each patient's own progress
CMP continuous passive motion, *ROM* range of motion
[a]In the case of myotendinous operations, active muscle work must be avoided for at least 3 weeks
[b]In the case of osteotomy or arthrodesis, the discharge time stated by the orthopedic surgeon must be observed

guidelines for a rehabilitation program after joint surgery without complications in patients with hemophilia are shown in the Table 12.5.

12.5 Most Commonly Used Rehabilitation Techniques

The most commonly used rehabilitation techniques are described below.

12.5.1 Prevention of Venous Thrombosis

In addition to strict hematological control, early mobilization, intermittent pneumatic compression therapy, and the use of compressive elastic stockings have been shown to be effective in preventing deep vein thrombosis. Other physical measures such as voluntary muscle contraction and massage therapy to improve circulation may also be used.

12.5.2 Pain Relief

Pain relief, which facilitates early mobilization and the recuperative process, is usually achieved with oral medication, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is avoided. The person with hemophilia should be taught how to control pain during the postoperative phase [2]. Currently the use of multimodal analgesia has shown to be very effective for controlling postoperative pain. Other analgesic control techniques are periarticular injections, continuous epidural anesthesia, and peripheral nerve blocking [15]. Intravenous patient-controlled analgesia is also a very effective method [2]. After the acute phase, physical pain control techniques, such as TENS (transcutaneous electrical nerve stimulation), may be used.

12.5.3 Cryotherapy

Cryotherapy on the area operated on is recommended for 20–30 min, three to four times a day after the physiotherapy session or the continuous passive mobilization. During the first 48 h after surgery, it can be applied for more time, in order to reduce bleeding and pain. Cryotherapy is currently under debate in patients with hemophilia due to its potential risk of prolonged bleeding [16].

12.5.4 Early Mobilization

For joint mobility to be recovered, the various techniques currently used must be applied. Manual joint mobilization by an experienced physiotherapist will be essential. In the case of the knee, these movements should be done by manual control of the patella.

The use of continuous passive motion (CPM) is especially appropriate for patients undergoing arthroplasty of the knee. It is recommended from the first day, for a minimum of 3 h, three times a day, with a frequency of one cycle per minute and flexion limited to 40° for the first 3 days, to pre-

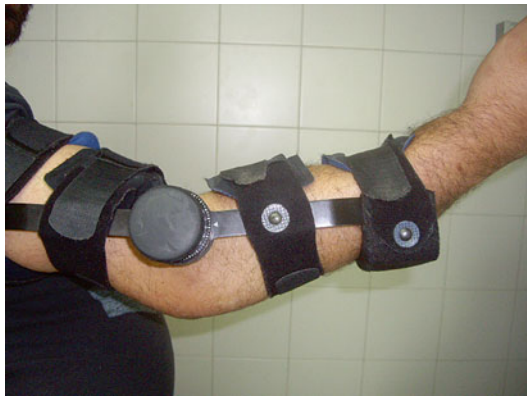

Fig. 12.2 Elbow hinge orthosis that allows progressive extension of the joint in a controlled manner after joint surgery. It is very useful in joints with significant risk of developing stiffness in bending. Should be used during those periods of the day when the patient is at rest

vent ischemia of the wound. The range of motion is gradually increased, attempting to reach flexion of 90° on the 7th day [17]. A systematic Cochrane review concludes that this treatment helps reduce the patient's fear of physical treatment and decreases the need for manual treatment. It does not, however, have clinically important effects on active knee flexion ROM, pain, function, or quality of life to justify its routine use [18].

In case of arthroscopy, recovery of mobility should not be a problem unless there are additional complications. On the other hand, in patients on whom arthrodesis has been performed, joint mobilization is contraindicated.

12.5.5 Orthoses

In those joints for which there is a significant risk of developing a flexion contracture, a hinged orthosis that allows the joint to be gradually extended in a controlled manner is very useful [2]. This device should be used during those periods of the day when the patient is at rest (including the night) (Fig. 12.2). Custom-made plantar orthoses or rocker soles are also useful. They are frequently prescribed to facilitate the mechanics of support and setting off in patients who have undergone ankle arthrodesis.

12.5.6 Soft Tissue Release

The risk of developing adhesions and retractions of soft tissues must be reduced as much as possible, because they can result in significant limitations to the joint. Manual techniques to release soft tissues are fundamental to preventing these adhesions and retractions developing. In the knee, for example, gentle patellar mobilization, both vertically and laterally, will decrease the risk of fibrosis in the "patellar retinacula". Once the wound is closed, techniques to release the scar and the extensor apparatus will be indicated.

12.5.7 Muscular Work

Improving muscular trophism is essential at all stages of the rehabilitation program and can be worked on using different methods.

Kinesitherapy techniques can improve various parameters for skeletal muscle, such as strength, power, and resistance. There are different types of contractions and ways of working, which will be combined, based on the specific objectives pursued [19]. Contractions can be isometric, isotonic, or isokinetic. Isometric contractions are appropriate immediately after surgery, because they decrease the risk reflex inhibition of the muscles without risk to joint structures. Isokinetic exercises have shown significant efficacy in terms of muscle strength, when compared with other methods [20]. If there is pain, limitation of range of motion, and significant swelling, isokinetic work and evaluations are contraindicated. When muscle and/or tendons have been operated on during the surgery, muscular work is not appropriate in the initial stages. There is not sufficient data to recommend routine use of neuromuscular electrostimulation, although it should be prescribed in cases of marked muscular hypotrophy, reflex inhibition of the muscle, or when active extension is limited [21]. It is intended to complement the benefits of voluntary muscular activity. It must be performed with active co-contraction (simultaneous voluntary muscle contraction) of the muscle group stimulated.

12.5.8 Proprioceptive Training

Proprioception is a kinesthetic skill that involves a complex neuromuscular and articular process in which sensory afferent nerves and motor efferent nerves are interrelated [22]. It is essential that this skill is recovered in order to be able to offer adequate static and dynamic stability to a joint complex, optimizing the energy consumed [23]. Rhythmic stabilization exercises, postural control exercises, and postural balance exercises, in different support planes, are very useful in this regard (Fig. 12.3).

12.5.9 Weight-Bearing

In terms of weight-bearing, transfers and gait reeducation will start in accordance with the timings agreed with the orthopedic surgeon, and this generally depends on the type of operation performed. For example, in the case of arthroscopic synovectomies or arthroplasties, partial weight-bearing can be authorized after 48 h, while a corrective osteotomy or ankle arthrodesis may require that the limb is kept non-weight-bearing for 6 weeks. In patients who have undergone elbow surgery, the use of an arm to sit up, make transfers, or use crutches may be limited for up to about 6 weeks; this must be taken into account in patients with musculoskeletal disorders in the lower limbs [5].

Fig. 12.3 Proprioceptive exercise with a ball by hemophiliac patient after arthroplasty of the right knee. Aims to provide adequate static and dynamic stability to a joint complex, optimizing the energy consumed

12.5.10 Gait Reeducation

From the start of weight -bearing being applied, the move to a bipodal weight distribution and gait reeducation must begin, with a progressive reduction in the use of support devices (walker, crutches). There will also be training in getting past obstacles, ramps, and stairs.

12.5.11 Occupational Therapy

Occupational therapy is especially designed for patients who have undergone upper limb surgery and those with difficulty in carrying out self-care tasks (personal hygiene, getting dressed, feeding, et cetera) since it reeducates in arm movements and basic everyday activities.

12.5.12 Other Techniques

During the rehabilitation period other techniques may be included, such as early hydrokinesitherapy and pedalling a stationary bicycle to improve coordination and muscle response. Therapeutic ultrasound can be used in pulsed mode with non-thermal effect in the initial postoperative stages and/or in continuous mode with thermal effect during scarring. Medium-level laser therapy (below 100 MW) could be used on the patient postsurgery, fundamentally for analgesic and anti-inflmmatory purposes; additionally, it will also improve tissue repair mechanisms [24].

12.6 Special Considerations

Postoperative rehabilitation on patients with hemophilia is effective, safe, and viable. It has been published that, in case of knee arthroplasty, the level of long-term satisfaction was rated as good in 72 % of cases and excellent in the remaining 28 % [25].

The functional outcomes of joint surgery in patients with hemophilia are not commonly as good as in the non-hemophilic population due to preexisting problems in other structures of the musculoskeletal system.

Although the general recommendations for rehabilitation after joint surgery in people with hemophiliac arthropathy have been mentioned previously, it must be borne in mind that there may be patients with special clinical circumstances that require treatment modifications, as discussed below.

One must consider the possibility of postoperative complications appearing in the short term, such as the intra-articular bleeding or postoperative hematoma that is typical of cases in which hemostatic coverage is inadequate, which may require drainage.

The most common complication that can lead to catastrophic failure is infection. This can occur in the short or long term after the intervention. The risk of an infection during the immediate postoperative period for a person with hemophilia should not be higher than that for the general population, if proper asepsis and hemostatic coverage have been maintained. However, it is well documented that people with hemophilia are at increased risk of secondary infection occurring later [2]. The reason for this increased risk is not clear. Sometimes, what causes a delayed infection is bacteremia from a distant or local infection [2].

Another relatively common problem is the inability to recover mobility, on many occasions resulting from stiffness that predated the operation (it is usual in cases of advanced hemophilic arthropathy). Fixed deformities in flexion or extension are associated with higher levels of pain, abnormal gait, difficulty in managing stairs, and worse outcomes in terms of the functional scales [26]. With the rehabilitation program, muscular improvement occurs during the first 6–12 months after the surgery, although a residual muscular deficiency usually persists for many years [27]. People with hemophilia with an arthropathy that has been operated on almost never reach the muscular strength of non-hemophiliac subjects of the same age group.

Other rare complications may also occur, such as skin lesions (delayed scarring, suture dehiscence, prolonged secretion, or cutaneous necrosis), nerve paralysis, complex regional pain syndrome, recurrent synovitis, heterotopic calcifications, or vascular complications.

In comparison with arthrotomy, arthroscopy simplifies the postoperative period and reduces the risk of the aforementioned complications. However it is imperative that, in all cases, the patient is closely monitored during the postoperative rehabilitation process.

In cases where multiple procedures have been carried out during surgery, it should be borne in mind that the expected rate of complications is higher, and therefore, the very best conditions for rehabilitation are required (factor, asepsis). Currently no guides have been developed for this type of procedure in patients with hemophilia [28].

12.7 Criteria for Discharge from Rehabilitation

The rehabilitation therapy should be continued until the physical and functional objectives proposed have been achieved.

While the patient is in hospital, fast-track discharge is a priority, i.e., discharge to the home as soon as possible, once hemostatic control has been established and the rehabilitation program has begun, following the basic guidelines for physiotherapy. It has been proposed that hospital discharge should be based on the following rehabilitative criteria: ability to move from supine to sitting and sitting to standing (and vice versa) and ability to walk at least 30 m with or without crutches, up and down a stretch of stairs [29]. These objectives are achieved in a few days.

The patient will then continue to follow the rehabilitation program on an outpatient basis. The patient is considered to have fulfilled the definitive therapeutic goals when the criteria outlined in the Table 12.6 have been met. These objectives may take between 6 and 12 weeks to achieve, depending on the patient's characteristics and progress. If the patient's progress is very satisfactory and progress beyond the established

Table 12.6 Criteria for discharge from rehabilitation after joint surgery in patients with hemophilia

Ranges of motion (ROM) in elbow (extension −30°, flexion 130°, supination 50°, and pronation 50°), in knee (full extension, flexion 90°), in ankle (dorsiflexion 15° plantar flexion 30°, plantigrade if arthrodesis)
Sufficient muscle strength to allow the aforementioned ROM against gravity
Make transfers
Walking with or without the help of crutches
The ability to go up and down stairs
Independence for activities of daily living
Knowledge of guidelines and exercise program
Adaptation to support devices if necessary (orthoses, footwear)

criteria is foreseen, the treatment may be prolonged in order to maximize the results of the surgery. When discharged from rehabilitation, patients must be well aware of the recommendations and guidelines and exercises that they must follow in their usual environment [9]. Patients must be motivated to continue with a low-impact aerobic physical activity after surgery, which will help them to maintain the recovery achieved and improve cardiovascular fitness, bone quality, and muscular strength. Swimming, static cycling, or daily walking in the flat is recommended [30]. In some cases, if a reversal of the improvement achieved is observed, another cycle of physiotherapy may be necessary [9].

Close postoperative monitoring must be carried out for at least the first 6 months. The most significant recovery is observed after 3 months. However, for up to a year after the operation, clinical and functional improvements may be observed.

12.8 Quality of Life

Quality of life is a multidimensional construct that includes the individual's physical, emotional, mental, and social well-being. Quality of life may be measured using generic or specific questionnaires. The first published data using generic questionnaires date from 1990. Various measuring instruments are currently available for children and adults, which take age and mental development into account. Operations that have good functional results not only improve physical but also emotional and social well-being [31].

Conclusions

In surgery to correct hemophiliac arthropathy, rehabilitation is fundamental to achieving the best functional outcome possible. It is essential to ensure good coordination between the orthopedic surgeon, hematologist, and the rehabilitation team for a suitable treatment program to be developed. The patient´s collaboration and motivation are other key factors in the prognosis.

Since there are multiple surgical options for the different joints, rehabilitation must always be customized to the individual. We must bear in mind that patients with hemophilia who undergo surgery usually present other polyarticular musculoskeletal problems in other parts of the body, which must also be addressed by rehabilitation treatment.

Successful outcomes in patients with hemophilia operated on for articular pathology depends on factors such as the selection of the patient, their expectations of improvement, the choice of surgical technique, hemostatic coverage during and after the procedure, the timing of the intervention, the rehabilitation treatment, and prevention of complications.

Preoperative goals of rehabilitation are to inform the patient about the entire process; to prescribe orthoses, support devices and adjustments that could be needed in the postoperative period; and to inform the patient with the aim of going to the surgical procedure in the best possible physical situation. The general objectives of rehabilitation after surgery are to: control pain, release soft tissues, recover joint movement, improve muscle trophism, train proprioception, and reeducate the gait and everyday activities-in sum, to regain functionality.

In order to increase the chances of a successful outcome and reduce the risks, these procedures should be performed in hospitals that have an experienced team in the management of patients with hemophilia.

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13 The Analgesic Efficacy of a COX-2 Inhibitor (Oral Celecoxib) in Adult Hemophilic Patients and Intense Joint Pain Secondary to Advanced Hemophilic Arthropathy

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and Víctor Jiménez-Yuste

13.1 Introduction

In 2006 Tsoukas et al. published a study where they showed that etoricoxib, a selective cyclooxigenase-2 (COX-2) inhibitor with anti-inflammatory activity, was more effective than placebo in the treatment of hemophilic arthropathy and that it was a safe and well-tolerated drug [1].

The purpose of the present chapter is to compare the analgesic efficacy of a COX-2 inhibitor (oral celecoxib) associated with oral paracetamol to that of oral paracetamol alone in adult hemophilic patients with hemophilia A and intense joint pain secondary to advanced hemophilic arthropathy (AHA).

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13.2 Review of the Literature

Hemophilic arthropathy often produces a severely painful disability in the majority of hemophilic patients [2]. Management of chronic hemophilic arthropathy is difficult. Analgesics may be used for pain relief, but their long-term use may result in dependence. NSAIDs have been used frequently in patients with coagulation disorders, albeit carefully as they inhibit platelet function [3, 4]. Nonetheless, the results of NSAIDs use have not been published.

Selective cyclooxigenase-2 inhibitors (COX-2), which inhibit the COX-2 enzyme in preference to COX-1, do not interfere with platelet thromboxane synthesis and therefore do not impair platelet function [5]. Moreover, COX-2 inhibitors entail a lower risk of gastrointestinal complications than traditional NSAIDs [6, 7].

Selective COX-2 inhibitors have been shown to be effective for pain relief and inflammation in cases of osteoarthritis, without affecting platelet function [5, 8]. COX-2 inhibitors are generally well tolerated, although Tosukas et al. reported a higher proportion of patients exhibiting adverse effects in the COX-2 inhibitor group than in the placebo group [1].

Intra-articular hemorrhage is a common finding in patients with hemophilic arthropathy. However, agents that decrease platelet aggregation (aspirin and NSAIDs) may influence the number or

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_13,

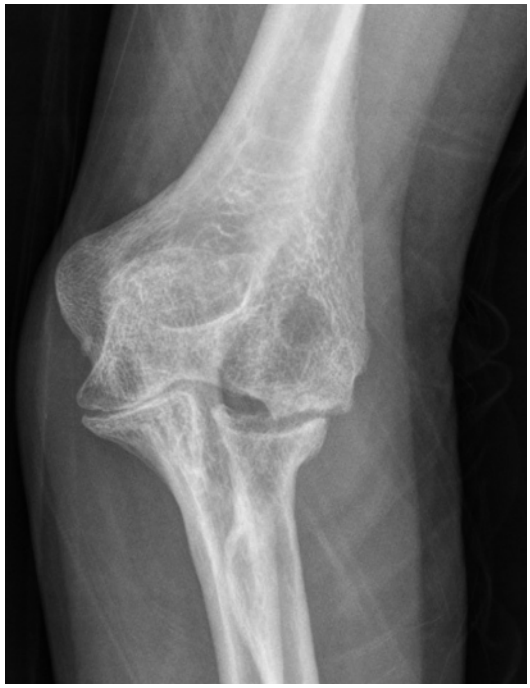

Fig. 13.1 Advanced hemophilic elbow arthropathy in an adult hemophilic patient in our study who presented with intense joint pain

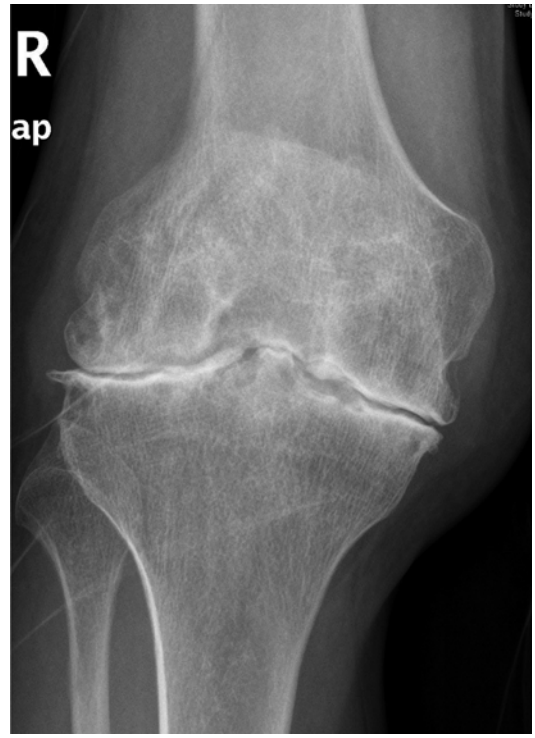

Fig. 13.2 Knee from an adult hemophilic patient in our series showing very advanced hemophilic arthropathy (AHA) associated with intense joint pain

severity of bleeding episodes and, therefore, the amount of deficient clotting factor required.

The literature presented herein suggests that treatment with COX-2 inhibitors is not associated with an increased incidence of hemarthrosis in patients with hemophilic arthropathy.

13.3 Authors' Experience

Sixty patients with hemophilia A and intense AHA-induced joint pain (Figs. 13.1, 13.2 and 13.3) were analyzed in order to determine the degree of pain relief provided by celecoxib. Patients were randomly divided into two groups of 30 patients each: a study group (Celebrex, Pfizer Laboratories, La Moraleja, Madrid, Spain) and a control group (without Celebrex). Patient inclusion criteria are displayed in Table 13.1.

Over a period of 2 months, patients in the control group (30 patients) were subjected to secondary hematologic prophylaxis (intravenous infusion of 3,000 IU of factor A/three times a week) combined with 650 mg/every 6 h of oral paracetamol (Gelocatil 60 mg, Laboratorios Gelos SL, Esplugues de Llobregat, Barcelona, Spain). The drugs were administered in 15-day cycles, with a 15-day resting period between cycles. Seventeen knees, nine elbows, and four ankles were treated. Mean patient age was 25.4 years (range: 21–50 years).

The study group (celecoxib) also included 30 patients, who were administered the same treatment as patients in the control group over 2 months, but with the addition of oral celecoxib (200 mg/once a day over 15 days followed by a 15-day resting period after which the cycle was repeated). Sixteen knees, eight elbows, and six ankles were treated. Mean patient age was 23.7 years (range: 20–58 years). Evaluation of pain was carried out by means of a visual analog scale (VAS, 0–100 mm,

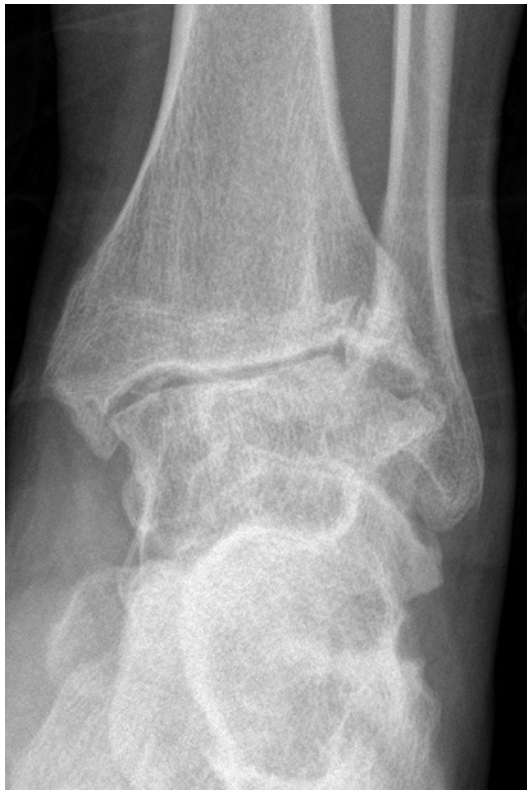

Fig. 13.3 Advanced hemophilic ankle arthropathy in an adult hemophilic patient in our study, who complained of intense joint pain

Table 13.1 Inclusion criteria for the study

Patients with severe hemophilia A (<1 % factor VIII)
Age >18 years
Advanced hemophilic arthropathy (AHA) as detected by radiology (over 10 points on Peterson's scale)
Joint pain >40 mm in elbows, knees, or ankles
Absence of hemarthrosis and synovitis (as determined on ultrasonography) at the time of inclusion into the study

where 0 indicated no pain and 100 the worst imaginable pain) prior to treatment and at 2 months' follow-up (treatment completion). Pain relief was considered poor when the treatment resulted in a decrease of less than 10 points on VAS, fair when the decrease was between 11 and 20 points, good when the reduction was between 21 and 40 points, and excellent when a decrease of between 41 and 60 points was obtained.

Descriptive and analytical statistics were used for data analysis. Results where $p<0.05$ were considered significant. The SPSS 15.0 statistical package for Windows was used for the analysis.

Results of control group: the pretreatment pain score was 73.4 (range: 45–95). The posttreatment pain score was 37.3 (range: 25–35). Results in this group were excellent in 11 cases, good in six, fair in eight, and poor in five. No differences were observed between the different joints (elbows, knees, ankles) with respect to those results. No complications were reported in this group.

Results of study group (celecoxib): the pretreatment pain score was 74.2 (range: 40–95). The posttreatment pain score was 15.9 (range: 10–20). Results in this group were excellent in 17 cases, good in nine, fair in two, and poor in two. No differences were observed between the different joints (elbows, knees, ankles) with respect to those results. Of the 30 patients in this group, two (6.6 %) reported a mild headache, which was associated with the use of celecoxib.

Table 13.2 shows the mean pre- and posttreatment pain scores in the two groups analyzed, as well as the degree of pain relief obtained (poor, fair, good, excellent) in both groups. Statistical analysis showed that pain improved significantly more in the celecoxib group (study group) than in the control group.

Table 13.2 Mean pre- and posttreatment pain scores and degrees of pain relief (excellent, good, fair, poor)

Criteria	Mean pretreatment pain	Mean posttreatment pain	Results
Control group (No celecoxib)	73.8	37.3	Excellent, 11; good, 6; fair, 8; poor, 5
Study group (Celecoxib)	74.1	15.9	Excellent, 17; good, 9; fair, 2; poor, 2

Conclusions

Advanced hemophilic arthropathy (AHA) is often accompanied by intense joint pain in most adult hemophilic patients. NSAIDs have been used frequently in hemophilic patients, albeit cautiously as they inhibit platelet function. In this chapter we have analyzed celecoxib's analgesic efficacy in adult patients with hemophilia A and painful AHA. Sixty adult hemophilic patients were randomized into two treatment groups. In the study group (30 adult patients), oral celecoxib was administered in association with oral paracetamol. In the control group (30 adult patients), only oral paracetamol was used (same dose). The secondary hematologic prophylaxis protocol used was identical in both groups for the entire duration of the follow-up period (2 months). At 2 months, remission of pain was assessed comparing post- with pretreatment pain scores on a visual analog scale (VAS). Joint pain in the celecoxib group improved significantly more than in the control group. Two patients in the celecoxib group reported mild drug-induced headache. In conclusion, celecoxib has been shown to be a highly effective anti-inflammatory treatment for joint pain in adult patients with hemophilia A and AHA.

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Anesthesia in Orthopedic Surgery of the Adult Hemophilia Patient

14

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14.1 Introduction

Hemophilia is classified into the diseases that cause disruption in normal blood clotting. It is an inherited X-linked disease, which produces a deficit in coagulation factors such as factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia A has a higher incidence (1 case per 5,000 males) than hemophilia B (1 case per 32,000 men). The current prevalence of hemophilia in the world is around 400,000 patients, of which 85 % are type A hemophiliacs.

The main clinical manifestation of hemophilic patients is the tendency to bleed, which usually begins in childhood. There are several degrees of hemophilia, depending on circulating factor levels, which are correlated with bleeding manifestations (Table 14.1).

Most clinical manifestations are related to articular bleeding (70–80 %) or muscle hematomas (10–20 %); fortunately severe bleedings that compromise the patient's life (in the nervous system) are rare (less than 5 %). The most commonly affected joints are the ankles, knees, and elbows [2].

One of the most frequent limitations in life's quality of hemophilic patients is problems associated with repetitive articular bleeding. Intraarticular bleeding disrupts the normal functioning of the articular cartilage, resulting in an early arthropathy with great limitation for the patient due to pain and secondary functional impotence; this situation leads these patients to be subsidiary of surgeries with high risk of perioperative bleeding, such as total knee replacement, as well as others with lower risk of bleeding, such as arthroscopic synovectomies.

The success of these interventions lies in the multidisciplinary approach between the orthopedic surgeon, anesthesiologist, and hematologist in a reference center with experience in the treatment of hemophilia [3].

Table 14.1 Grade of hemophilia according to the percentage of circulating factor and clinical manifestations of the disease [1]

Severe grade	Less 1 % factor <0.01 Ui/ml	Spontaneous bleeding Joints and muscles
Moderate grade	1–5 % factor 0.01–0.05 Ui/ml	Occasional spontaneous bleeding. Bleeding with surgery or trauma
Mild grade	5–40 % factor 0.05–0.4 UI/ml	Bleeding only with surgery or trauma

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_14,

14.2 Preoperative Approach

14.2.1 History

In the anamnesis we must ask the patient about bleeding frequency, trying to find the location and especially the triggering effect of it, which will guide us (along with lab tests) about the degree of factor deficiency.

We will ask about transfusion-related infections, such as hepatitis C virus or HIV. We must also corroborate the presence of other associated diseases such as:

- Hypertension is more prevalent in hemophilic patients than in the general population; an optimal control previous to the surgical intervention is very important [4].
- Dyslipidemia is less frequent in hemophilic patient than in general population [5].
- On the other hand, a decreased risk of death from ischemic heart disease in the hemophilic population compared to the general population has been described, although it is increasing in the last years. There is an association between the use of factor and myocardial infarction. The presence of myocardial infarction in a hemophilic patient includes individualized attention due to the fact that antiplatelet therapy is not indicated [6].

14.2.2 Laboratory Tests

- Platelet count, hemoglobin level, complete biochemical analysis, and clotting tests with factors VIII or IX levels
- Presence of inhibitors

14.2.3 Preoperative Pain Treatment

Most surgical interventions in hemophilic patients are orthopedic surgeries, due to an advanced hemophilic arthropathy. Before coming to surgery, these patients have been treated with analgesics, with varying doses of morphine, and when pain is not controlled despite them, the orthopedic intervention is indicated [7]. It is important to corroborate in the preoperative evaluation, the usual dose of morphine consumed by the patient in order to administer it postoperatively. Table 14.2 summarizes the common analgesics used in hemophiliacs.

Table 14.2 Common analgesics used in hemophilic patients [8, 9]

1° step	Acetaminophen
2° step	COX-2 inhibitors or acetaminophen-codeine or acetaminophen-tramadol
3° step	Morphine in variable dosage (morphine, oxycodone)

Pain management is done, as the intensity increases. In the second step COX-2 are indicated, which must be prescribed with caution in patients with hypertension or renal dysfunction. Other anti-inflammatory are not used in hemophilic patients due to the bleeding risk [10].

14.2.4 Physical Examination

Once the anamnesis is concluded and the regular medication consumed registered, we will focus on the physical examination, with special attention to the airway exploration, as these patients are usually candidates for general anesthesia. The management of the airway should be exquisite, with a well-organized intubation plan. It includes different options and the use different devices, due to the fact that in these patients multiple intubation attempts can trigger mucosal bleeding and endanger the patient's life. Airway exploration test on their own has limited sensitivity and specificity, but when used in combination, their predictive value increases [11].

14.2.5 Final Considerations in the Preoperative Evaluation

As final considerations in relation to the preoperative evaluation, the following conditions shall apply:

- Advice the complete surgical team (anesthesiologist, hematologist, and orthopedic surgeon) when scheduling the surgery so the whole team is aware about the patients pathology.

- Confirm with the hospitals pharmacy enough factor availability for a proper perioperative management.
- Confirm with the blood bank that blood products needed for surgery are reserved.

14.3 Perioperative Management

There are two important situations, hemostatic considerations and different anesthetic options.

14.3.1 Hemostatic Considerations

We must pay attention to the presence of inhibitors and to the level of the deficient factor.

Patients Without Inhibitors

The objective is to obtain an adequate level of deficient factor so the surgery can be performed. The hematologist is the main responsible of obtaining an appropriate level of preoperative factor and does also keep it during all the surgery and the postoperative period. Table 14.3 shows the percentage of factor needed in each phase and the duration of the treatment with factor depending on the type of surgery.

The reference value of 60–80 % factor just prior to anesthetic induction is the value the anesthesiologist should check in order to carry out the surgery.

Intravenous administration of concentrated either recombinant or plasma-derived factor is the correct way to get a proper percentage of factor for an adequate surgery hemostasis [13].

Table 14.3 Percentage of factor and maintenance depending on the type of surgery [12]

	% factor target	Maintenance days
Major surgery		
Preoperative	60–80 %	
Postoperative 1	30–40 %	1–3 days
Postoperative 2	20–30 %	4–6 days
Postoperative 2	10–20 %	7–14 days
Minor surgery		
Preoperative	40–50 %	
Postoperative	20–50 %	1–5 days

The half-life of factor ranges between 8 and 12 h. In the case of factor VIII, each unit per kg of patient weight given intravenously increases the plasma level about 2 IU/dl [14].

In case of unavailability of concentrated factor, cryoprecipitate or fresh frozen plasma can be administered. The initial dose of fresh frozen plasma administered is 15–20 ml/kg [15].

Patients with Inhibitors

Inhibitors are IgG antibodies that neutralize coagulation factors. They are more common in hemophilia A, with an incidence of 20–30 %, whereas in hemophilia B, they range from 5 to 10 %. They are more common in severe grades of hemophilia than in cases of mild to moderate hemophilia [16].

It is particularly important in the perioperative period, because the exposition to high doses of deficient factor, as it occurs in this period, can precipitate the antibody appearance. It must be suspected when the response to the factors infusion decreases; accurate diagnosis is determined with a laboratory test [17].

If inhibitors appears, depending on the range of them, higher doses of factor (in case of bit inhibitor) or recombinant activated factor VII will be necessary, requiring even activated prothrombin complex in cases of high amount of inhibitor [18, 19].

Other therapeutic options to improve hemostasis, like desmopressin and antifibrinolytic therapy have low utility in major surgery. Desmopressin is useful to prevent bleeding in mild or moderate hemophilia A [20]. Antifibrinolytics, in particular tranexamic acid, are used to reduce bleeding in case of dental procedures [21].

14.3.2 Anesthetic Management

Hemostatic factor levels should be checked previously to the anesthetic induction. In relation to the patients monitoring, overall 5-lead electrocardiogram, peripheral oxygen saturation, and noninvasive blood pressure are used. Invasive monitoring is not indicated just because it is a hemophilic patient, only in those cases in which size of the surgery requires it.

A peripheral venous access with high gauge, which is different to the one used for the factors

infusion, is recommendable. In the case in which the use of a central venous line is indicated, the hemostatic level must be around 80 % and be preferably punctured under ultrasound guidance to minimize mistake punctures and subsequent bleeding [22]. There is no contraindication to the use of any hypnotic agent in both the induction and maintenance; the choice is anesthesia based in analgesia with opioids.

Nasal intubation should be avoided whenever possible, as also multiple tracheal intubation maneuvers, in order to minimize the risk of mucosal bleeding. A plan should be done in the preoperative evaluation intubation in case of a scheduled or anticipated difficult airway, using a device that ensures intubation without multiple attempts.

Anti-inflammatory drugs should be avoided and postoperative analgesia based in opioids must be first option, ideally by pump intravenous infusion of morphine under PCA (patient-controlled analgesia) system, which has been shown to improve patient satisfaction and postoperative pain control compared to conventional opioid administration [23].

Neuraxial anesthesia has numerous benefits over general anesthesia, such as better pain control with fewer side effects from opioids administration and improved patient recovery [24]. There are numerous guidelines that govern the use of neuraxial anesthesia in patients taking various drugs affecting coagulation, marking a time of suspension of the drug in order to perform the technique with minimal risk of bleeding, since the appearance of a neuraxial hematoma has consequences disastrous for the patient [25].

Some authors reported 107 cases of neuraxial anesthesia in hemophilic patients. Most of them were diagnostic lumbar punctures, but 35 of them corresponded to punctures for lower limb surgery, and 18 epidural punctures, including 7 for labor. In none of these cases complications were found. It is important to say that all of them were performed with factor levels in hemostatic range for surgery. However, a case of neuraxial puncture in a not known hemophilic patient was described, with the appearance of secondary spinal hematoma and consequent paraplegia [26].

Regarding the use of peripheral nerve blocks in hemophiliacs, Vanarase et al. reported 15 cases of nerve blocks for postoperative analgesia in knee replacement without any complications [27] and Kang described the use of an axillary catheter for elbow surgery with better postoperative analgesia and faster rehabilitation without development of any complications [28]. The use of nerve blocks reduces postoperative analgesic requirements and decreases the potential adverse effects of systemic medication [29]. As in neuraxial analgesia, no recommendations exist about the level of factor required for a safe performance, being compression to prevent relevant bleeding difficult in both techniques. Table 14.4 shows the risk of bleeding in neuraxial anesthesia and nerve blocks depending on the type of block [30].

Table 14.4 Bleeding risk in neuroaxial puncture and nerve blocks due to type of block [30]

	Block category	Block type
High risk	Epidural catheter	
↑	Epidural single shot	
	Paravertebral	Paravertebral block
		Lumbar block
		Deep cervical block
	Deep block	Gluteal sciatic approach
		Obturator block
		Infraclavicular and supraclavicular block
	Superficial perivascular block	Femoral block, sciatic block, interscalene block, axillar block
	Fascial block	TAP (transversus abdominis plane) block
	Superficial block	Elbow, wrist, ankle, interdigital block
	Local	
Normal risk		

Finally, the use of nerve blocks or neuraxial blockade has known benefits in the postoperative period, especially in orthopedic surgery; cases of hematomas related to these are rare, but this does not mean that they do not occur. There are no recommendations regarding the level of security to perform them in the hemophilic patient. The use of a catheter involves a greater risk, due to the risk of bleeding itself and because the level of factor changes with the passage of days after

surgery, and it can be much lower than the surgery level, increasing the risk of bleeding if the catheter is removed at this time.

Conclusions

Hemophilic patients undergoing orthopedic surgery are susceptible of bleeding complications during all the perioperative period. The majority of patients who undergo surgery are known hemophiliacs; this means that the surgery is performed with the proper dose of the deficient factor. The most common anesthetic technique used in hemophiliacs is general anesthesia; it causes minimal bleeding complications, including at the neuraxial level. In recent years, the use of peripheral nerve blocks in patients with adequate hemostatic factor level has been documented, without occurrence of bleeding complications. Currently, however, general anesthesia remains the technique of choice in hemophilia patients undergoing orthopedic procedures.

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Pharmacoeconomics of Orthopedic Surgery in Hemophilia

15

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15.1 Introduction

Hemophilia is a genetic disease characterized by a deficit or absence of a clotting factor. This deficit or absence is due to a genetic mutation occurring in the X chromosome. The disease may be classified into hemophilia A when there is a deficit of factor VIII (FVIII) and hemophilia B in the case of a deficiency of factor IX (FIX). The clinical manifestations of both deficits are recurrent articular bleeds and severe joint damage eventually [1]. The number of bleeding episodes and their severity are related to the activity of the deficient factor in plasma [2]. Hemophilia can be classified into:

Severe hemophilia, when the coagulation factor activity is less than 1 %. It is usually characterized by the appearance of spontaneous bleeding episodes (muscles and joints).

Moderate hemophilia, when the activity of the coagulation factor is between 1 and 5 %. It is characterized by the occurrence of spontaneous bleeding episodes occasionally and also in cases of severe trauma or surgery.

Mild hemophilia, when factor activity exceeds 5 %. It is characterized by the occurrence of bleeding in traumatic episodes or during surgical procedures.

Bleeding episodes may occur anywhere in the body, but most of them take place in muscles and joints. Recurrent bleeds in the joints cause severe disability in the long term (hemophilic arthropathy). In some patients, limitation of articular mobility and joint deformity may require a surgical procedure, such as total joint arthroplasty. The joints most commonly affected in hemophilia patients are the knees, ankles, elbows, and hips [3, 4]. The management of patients with advanced hemophilic arthropathy is often complex, ranging from less invasive surgical techniques (radiosynovectomy) to more complex surgical techniques (total joint arthroplasty).

Any surgical procedure must be carried out under factor coverage (intravenous administration of the deficient coagulation factor). Hematological substitution treatment (secondary prophylaxis) without using surgical procedures may avoid new joint bleeds but will not solve the mobility problems already established. Secondary prophylaxis is very expensive due to the high cost of factor concentrates. Orthopedic surgical techniques may help to improve articular mobility, relieve patient pain, and halt recurrent bleeds in the affected joints. A strict control of hemostasis by means of intravenous infusion of the deficient coagulation factor, both in the perioperative and postoperative periods, is paramount to perform

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E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6_15, © Springer International Publishing Switzerland 2015

any orthopedic surgical procedure in a hemophilia patient. Such hemostatic control has a high economic cost. That is why the pharmacoeconomic analysis of orthopedic surgical procedures is very important in hemophilia. In fact, such a cost many times is not covered by some national health systems.

15.2 Economic Evaluations in Health Care

Healthcare systems in different countries need to address the growing demands with increasingly limited resources. In order to carry out this need, economic evaluations of health interventions must be performed. Economic evaluation studies are very important, but their implementation may be complex because they must quantify all factors involved in a particular surgical procedure. It is important to get a close view of the economic reality of a health intervention and also avoid overspendings.

Canada was one of the pioneering countries in health economic evaluations. The Canadian Coordinating for Health Technology Assessment (CCOHTA) defined health technology assessment as "the process of assessing medical technologies (devices, procedures, and drugs) and their use." In order to carry out the analysis of evaluation studies, CCOHTA published some "Guidelines for economic evaluation of pharmaceuticals." Such guidelines allow us to improve the methodology of various models of economic evaluation [5].

There are other national agencies that have established criteria for the selection and use of drugs funded by their national health systems. In Europe, they include the National Institute for Health and Clinical Excellence (NICE) in UK, the Scottish Medicines Consortium (SMC), the *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWIG) in Germany, and the *Haute Autorité de Santé* (HAS) in France.

In Spain, there is no official agency evaluating economic data of health interventions or medications. However, the Spanish Ministry of Health has published two reports that address economic evaluations. They are "Methods for the economic evaluation of new features" [6] and "Proposed guidelines for economic evaluation of health technologies" [7]. An important amount of Spanish economic resources are spent in drugs used in different diseases. This fact, together with the absence of a Spanish state agency performing economic evaluations, has highlighted the paramount role of Pharmacy Departments in Spanish medical centers. In fact, Pharmacy Departments look for pharmacological efficiency (greater therapeutic benefit at a lower cost) by means of pharmacoeconomic studies. Comparative studies of different therapeutic options, both in terms of costs and benefits, are particularly relevant [8].

15.3 Types of Economic Evaluations

The term "economic assessment" usually includes the economic comparison of different treatment options. However, other types of studies can help to improve the efficiency of drug therapies. Among these we must emphasize the analysis of the pharmaceutical bill and the budget impact studies. The latter are of great interest when the cost of a particular drug per patient is very high, thus producing a great economic impact on the pharmaceutical budget. This is what happens in hemophilia patients, because the cost of factor concentrates is very high, particularly when orthopedic surgery is carried out. More than 90 % of the cost of an orthopedic surgical procedure in hemophilia is due to the hematological treatment (consumption of factor concentrates).

A budget impact analysis is greatly appreciated by managers of health centers. This analysis helps us to quantify the deviation of a health intervention in relation to the one forecast for such a health intervention [9, 10]. In order to determine the budgetary impact, we must know the total number of patients undergoing a particular health intervention or the total number of health interventions. The estimation will let us know whether a health intervention meets expectations or needs a modification in the allocation of resources.

An economic evaluation includes a comparison of at least two alternatives and involves the analysis of both the costs and the consequences of the alternatives evaluated. The choice of a comparator is crucial to determine the incremental cost/effectiveness of a particular intervention. The comparator must be the best therapeutic alternative that could be used. If the economic assessment is based on clinical trials, the outcome variable must be efficacy; if it is based on data obtained in clinical practice, it must be effectiveness.

The resources spent should be specified in detail; moreover, the analyzed parameters should reflect the opportunity cost. It is defined as the economic cost of the best alternative possible. Sources of costs can be obtained from official publications, analytical accounts of health centers, and market prices.

Economic evaluations are classified into two categories depending on how they are analyzed and on how the results or benefits are evaluated. In cost/benefit analysis (CBA), the results are quantified in monetary units. In cost/effectiveness analysis (CEA), the results are measured in terms of efficiency or effectiveness. When CEA are adjusted to parameters of quality of life, they are called cost/utility analysis (CUA).

In CBA, the results of two or more alternatives are compared in monetary units, and the net value of a given alternative is obtained. This type of analysis is not useful in healthcare. The reason is that it is difficult to assign monetary values to health outcomes.

CEA evaluates the results in nonmonetary units. It can measure intermediate clinical outcomes, like the number of bleeds. It can also measure clinical outcomes, such as the years of life gained in case of orthopedic procedures. This type of economic evaluation compares two or more alternatives; that is why the ratio cost/effectiveness must be calculated incrementally. The result would be the ratio between the differences in treatment costs and the difference in the outcomes measured in nonmonetary units. The result of a CEA indicates the increased cost of an alternative therapy to obtain some units of health improvement expressed in clinical units, such as number of bleeds avoided or years of life gained.

CUA further contemplate quality of life. CUA implies that it is not the same to live with full health than with some disability. Therefore, CUA introduces a subjective parameter (quality of life). In these analyses the benefit obtained is measured in QALYs (quality-adjusted life years).

Table 15.1 shows the economic evaluation of a hemophilia patient using QALYs to calculate the cost/effectiveness ratio. The patient was an adult hemophiliac with advanced knee problems that required a total knee replacement (TKR). In this case there were four possible alternatives (Table 15.1):

1. No treatment, with no cost but 0 QUALYs.
2. Secondary prophylaxis (factor infusion 2–3 times per week to avoid joint bleeds) with an annual cost of € 200,000. In this case we estimate that the patient will gain 10 QUALYs. This alternative would cost € 200,000 more than alternative one (no treatment). Each QUALY would cost € 20,000.
3. On-demand treatment (factor infusion only during bleeding episodes), with a cost of € 100,000. In this case we estimate that the patient will gain 9 QUALYs.

Table 15.1 Costs, outcomes, and cost/effectiveness analysis of different treatment options for an adult hemophilic patient with severe knee arthropathy that eventually required a total knee replacement (TKR)

Alternatives	Costs (€)	Results (QALY)	Increase of costs	Increase of QALYs	Cost/effectiveness ratio (€/QALY)
No treatment	0	0	200,000	10	20,000
Secondary prophylaxis	200,000	10			
On-demand treatment	100,000	9	100,000	1	100,000
Secondary prophylaxis	200,000	10			
Secondary prophylaxis	200,000	10	100,000	10	10,000
Implantation of TKR	300,000	20			

QUALYs quality-adjusted life years

4. The fourth alternative would be to perform a TKR with an estimated cost of € 300,000 but with 20 QUALYs.

In this case the most favorable option from the pharmacoeconomic point of view would be the implantation of a TKR.

Cost/effectiveness studies have an important disadvantage: they are not valid to decide whether an alternative treatment must be performed because it is not the same to assume a cost in the context of economic bonanza than in times of recession. Economic evaluations are not intended to conclude whether a treatment can or should be used. They are intended to specify and compare costs and consequences, with the aim of facilitating the decision-making. The goal is to improve the efficiency of a particular therapy.

One issue to be considered in economic evaluations is the temporary space. For instance, the implantation of a TKR in a hemophilic patient has an immediate cost, but also long-term benefits. There is no doubt that immediate benefits are usually preferred. Benefits and costs, however, cannot be separated from the time period in which they occur. The application of the so-called discount rate in economic assessments incorporates the aforementioned temporary circumstances, as the costs and benefits that arise in the future are usually valued less. The discount rate applied varies between different countries but ranges from 3 to 5 %. This circumstance is very important when transferring the results of a pharmacoeconomic study in a particular country to another country, so the results should be interpreted with caution.

The robustness of the results in studies of economic evaluation is supported by sensitivity analyses. A sensitivity analysis is necessary in CEA analyses because the own nature of the studies assume values of variables that are not verified in any part of the analysis, creating uncertainties in its results. To minimize these uncertainties, we must compare the results of the variables involved with an estimation range, holding constant the other variables. If the incorporation of the various estimates does not substantially change the findings, it may be considered that the study has a high degree of reliability and its conclusions are sound.

15.4 Cost of Orthopedic Surgery in Patients with Hemophilia

Patients with hemophilia undergoing orthopedic surgical procedures should be treated throughout the perioperative period with the intravenous infusion of factor concentrates to control their hemostasis. The high cost of these drugs increases the cost of the process significantly. It is estimated that over 90 % of the total cost of the surgical procedures in hemophilia is due to the drug therapy used. In orthopedic surgery of hemophilia, the pharmacoeconomic analysis may ignore other associated costs. Thus, considering only the costs of factor concentrates, one can obtain a fairly accurate estimate of the cost of the surgical procedure.

Over the last 7 years our multidisciplinary hemophilia team has performed 60 surgical orthopedic procedures with a total cost of more than two million euros. Such procedures include arthroscopic debridements (knee, ankle) and TKRs and THRs. The cost of each of these procedures can be highly variable (Fig. 15.1).

A number of factors can influence on the variability of costs. The most important are: the severity of hemophilia, the patient's weight, the type of surgery, and the origin of factor concentrates used. The estimated cost of arthroscopic surgery in hemophilia ranges between 20,000 and 30,000 €, depending on the type of factor used in the intervention.

Most common surgical procedures in hemophilia patients are TKR and THR. The cost of these procedures ranges between 40,000 and € 50,000. THR is 2–3 % more expensive than TKR. Taking into account that the hemostatic protocols used in our center are very similar in THR and TKR, the variability in cost may be due to other factors such as patient

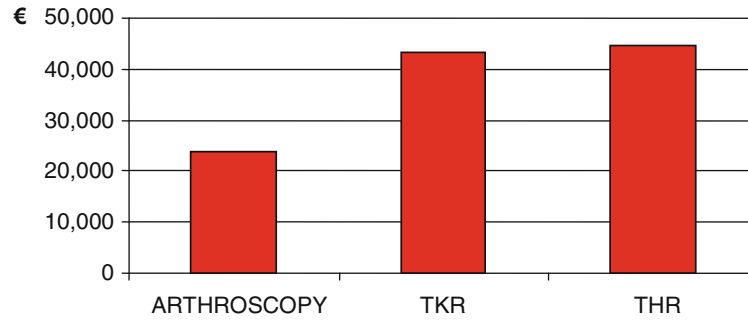

Fig. 15.1 Cost of some orthopedic procedures performed in our center (in euros). *TKR* total knee replacement, *THR* total hip replacement

weight, type of factor used, and days of postsurgical hematological treatment. It is important to emphasize that the aforementioned costs are related only to the perioperative period, not to the subsequent hematological treatment needed for postoperative rehabilitation (1–2 months).

15.5 Quality and Cost of Drug Replacement Therapy in Orthopedic Surgery in Patients with Hemophilia

Quality problems in drug therapy could be classified into three categories depending on the use of the resources: underuse, overuse, and wrong use.

15.5.1 Underuse of Resources

Underuse of resources can be defined as the failure to use a therapeutic procedure that had produced a clear benefit to the patient and also subsequent cost savings. Not performing a TKR in a hemophilic patient at the right time could imply drug overuse and extra resources because recurrent joint bleeds will require the administration of great amounts of factor concentrates, with a significant budgetary impact. However, a TKR or THR could halt recurrent bleeds in the target joint, saving a lot of consumption of factor concentrates. Although initially the surgical procedure implies a major economic cost, it can be repaid within a reasonable period of time with the improvement in the quality of life of the patient. In our center, orthopedic surgical procedures had a significant initial cost, but the consumption of factor concentrates is significantly reduced after surgery [11]. Moreover, we get a significant improvement in the quality of life of our patients.

15.5.2 Overuse of Resources

Overuse of resources must be understood as the administration of pharmacological resources in circumstances where the potential cost exceeds the potential benefits, thereby increasing the economic resources unnecessarily. In hemophilia patients undergoing orthopedic surgery, the administration of factor concentrates allows us to save costs by administering a lower amount of such factor concentrates. Proper monitoring of patients through protocols, including a drug-economic perioperative assessment, is essential to saving costs in the surgical treatment of hemophilia patients. The economic evaluation of this monitoring may allow cost savings in two ways: (1) Predicting costs and making the provision of drugs on a scheduled time. (2) The pharmacokinetic analysis will allow us to use the adequate amount of factor needed for each patient, based on an individualized drug clearance. Administration of factor concentrates by continuous infusion, based on individual pharmacokinetic parameters, may allow the patient to maintain constant plasma levels of factor. It will prevent peaks of clotting factor in plasma (Fig. 15.2).

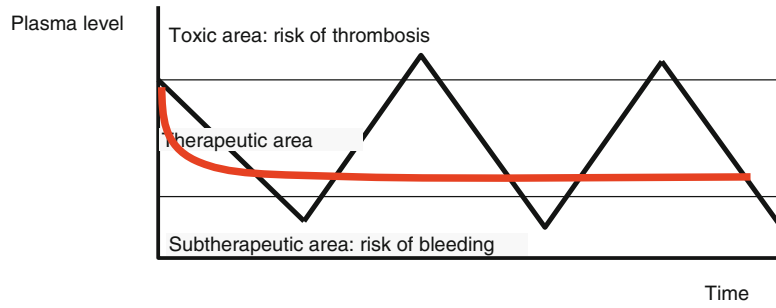

Fig. 15.2 Plasma level of factor concentrates via intravenous continuous infusion (*red*) and via intravenous bolus (*black*)

15.5.3 Wrong Use of Resources

The wrong use of a drug may cause complications and also lead to over-utilization of economic resources. An example of wrong use is the administration of low doses of clotting factor during surgery, causing re-bleeding of the surgical wound that may increase the risk of infection of the implanted prosthesis. In this case the potential savings produced by the administration of smaller amounts of factor concentrates would be cancelled for the subsequent reoperations needed to treat an infected prosthesis. Economic evaluations of different scenarios by means of decision trees will allow us to perform the best cost-effective therapeutic measure. In addition to important cost savings, we will get an improvement of the quality of life of our patients [8].

15.6 Economic Evaluations as a Tool in Decision-Making

Decisions to be made by the agents involved in a process of healthcare are often complex and subjected to doubts, risks, and uncertainties. These situations require the establishment of systematic procedures to facilitate the most suitable solution to each problem. Decision-making in the area of healthcare refers to any process by which a health professional or manager adopts a specific solution to a specific problem, choosing from among all the options the one which is most appropriate.

The logical sequence to be adopted in the process of decision-making, within a context of limited information would be the following:

(a) Identification and definition of the problem
(b) Strategic search for alternative solutions
(c) Evaluation of the benefits and risks of each potential solution
(d) Selection of the most suitable alternative

In hemophilic patients with advanced hemophilic arthropathy, we have two basic treatment options: maintenance of factor replacement therapy for life or performing some orthopedic procedure that may help to halt recurrent joint bleeds. We know that the cost of lifetime maintenance of factor replacement therapy may be higher than the cost of the surgical procedure. Patients with high consumption of clotting factor for recurrent joint bleeds due to hemophilic arthropathy could be good candidates for an orthopedic surgical procedure. Therefore, we must try to improve the quality of life of hemophilia patients but also minimize, if possible, the cost of their treatment.

15.7 Pharmacoeconomics and Health Management in the Pharmacological Treatment of Orthopedic Surgery in Hemophilia

Health is one of the cornerstones of the social structure of developed countries. Healthcare is one of the fundamental rights of citizens and therefore one of the most important commitments that governments must address through health managers. Healthcare involves three main levels:

(a) Macro-management: ministries and departments of health

(b) Middle management: managers of hospitals, drug information centers, and agencies for health technology assessment
(c) Micromanagement: heads of departments, clinical units, committees of pharmacy, and therapeutics.

Public financing of health is one of the most representative achievements of the welfare state. Its development has helped to improve health and prevent disease. A major part of the cost of healthcare of hemophilia patients is related to drug therapy (factor concentrates). Replacement therapy with factor concentrates and orthopedic surgical procedures have allowed us to decrease morbidity and mortality and also to improve the quality of life of our hemophilia patients.

Studies of cost of illness have been designed to evaluate the economic impact of healthcare. These studies, combined with epidemiological studies of morbidity and mortality, are very useful to know the magnitude of the cost of health. The economic evaluation of drugs allows us to identify, analyze and compare the costs, benefits, and risks of drug treatments. The cost/effectiveness ratio will let us face different treatment alternatives and also choose the efficient use of resources.

Clotting factors used in the treatment of persons with hemophilia cause a high economic impact in the public health system. Such impact is of great concern, not only for managers but also for professionals involved in the treatment of hemophilia. The Spanish universal public health system, which produces well-being but no economic benefit, is forced to minimize costs in order to ensure its survival.

Conclusions

Healthcare systems need to address growing demands with increasingly limited resources. In order to carry out this need, economic evaluations of health interventions must be performed. Their implementation, however, can be complex because they must quantify all factors that may be affected by a particular surgical procedure. There are other simpler studies that may provide a closer view of the economic reality of a health intervention, helping us to detect potential overspendings. An important amount of Spanish economic resources are spent in drugs used in different diseases. This fact, together with the absence of a Spanish state agency performing economic evaluations, has highlighted the paramount role of Pharmacy Departments in Spanish medical centers. In fact, Pharmacy Departments look for pharmacological efficiency (greater therapeutic benefit at a lower cost) by means of pharmacoeconomic studies. Comparative studies of different therapeutic options, both in terms of costs and benefits, are particularly relevant. A number of factors can influence the high cost of orthopedic surgery in hemophilia. The most important are: the severity of the disease, the patient's weight, the type of surgery, and the origin of factor concentrates used. The estimated cost of an arthroscopic debridement (knee, ankle) ranges between 20,000 and 30,000 €. Most common surgical procedures in hemophilia patients are total knee and hip replacement. The cost of these procedures ranges between 40,000 and € 50,000. It is important to emphasize that the aforementioned costs are only related to the perioperative period. Clotting factors used in the management of persons with hemophilia cause a great economic impact in the public health system. Our universal public health system must minimize costs to ensure its survival.

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Index

E.C. Rodríguez-Merchán (ed.), *Joint Surgery in the Adult Patient with Hemophilia*,
DOI 10.1007/978-3-319-10780-6, © Springer International Publishing Switzerland 2015