Musculoskeletal Aspects of Haemophilia

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To my wife (Hortensia) and the rest of my family
for their constant and patient support.
E.C. Rodriguez-Merchan

To my family for their continued forebearance,
love and encouragement.
N.J. Goddard

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Preface

Haemophilia is a lifelong inherited bleeding disorder characterized by severe, spontaneous bleeding resulting in chronic, painful joint deformities. Without treatment, individuals with haemophilia will die in childhood or early adulthood. Thus, in a monograph from the US by Carroll Birch in 1937, the life expectancy of a haemophilic patient was approximately 20 years, and it was rare for the patient to survive to the age of 40. This is in vivid contrast to a patient in London who died recently at the age of 85 years, having received a shoulder replacement several years earlier which had substantially improved his quality of life.

The development of safe and effective clotting factor concentrate has enabled the orthopaedic surgeon to approach the patient with haemophilia with almost the same security as a patient without a bleeding disorder. Large pool clotting factor concentrates manufactured from human plasma became available in the developed world in the 1970s, and from 1986 this has become relatively 'safe' from viral transmission; in particular there has been no transmission of HIV following treatment with virucidally treated factor replacement since 1986 anywhere in the world. More recently, the development of high-purity concentrates has enabled perioperative delivery of clotting factor by continuous infusion, giving added safety during the period of surgery and the possibility of more intensive physiotherapy postoperatively. The newer recombinant clotting factor concentrates are particularly easy to deliver by continuous infusion.

The large epidemics of transfusion-transmitted disease resulting from the widespread use of large pool plasma derived clotting factor occurred during 1961–86 for the hepatitis C virus (HCV) and 1978–86 for human immunodeficiency virus (HIV). Thus, the generation of haemophilic patients who had poor treatment in their childhood and consequently are now needing orthopaedic procedures such as joint replacement are the patients most likely to be infected with HCV and HIV. This has presented problems for the orthopaedic surgeon and his team – destroyed joints can bleed extensively! Nevertheless, there are no reported transmissions of HIV or HCV to the operating team from a haemophilic patient. There have been many needle-stick accidents requiring an intervention with anti-retroviral therapy for HIV which has

caused much physical and psychological morbidity. Clearly, there need to be rigorous operating procedures in place, and continuing vigilance. The advent of anti-retroviral therapy for HIV has the added concern of 'bleeding' in association with protease inhibitors reported in the haemophilic patient.

In parallel with the development of safe and effective clotting factor concentrates, the management of newly diagnosed children with haemophilia involves prophylaxis, or regular injections with clotting factor to stop bleeds, particularly joint bleeds. In well-resourced parts of the world this is performed using recombinant clotting factor for reasons of viral safety. This has enormous resource implications, and the cost–benefit analysis has to take into account that such individuals will grow up to expect a normal life and will not require expensive orthopaedic procedures. Although the use of continuous infusion can reduce by one-third the clotting factor concentrate used to cover a joint replacement, it still equates to about the average yearly use for an adult, that is 70 000 units, at a cost of approximately $20 000.

It has been suggested that worldwide 80% of those with haemophilia do not have access to adequate medical care. Many of those individuals are undiagnosed and untreated, and therefore suffer enormously. Often, expert orthopaedic care cannot be provided to the haemophilic patient because of the constraint of lack of clotting factor provision for economic reasons. There have been initiatives supported by the World Federation of Haemophilia and the fractionating industry to enable orthopaedic surgery to take place, and there are studies using continuous infusion with the maintenance of lower levels of clotting factor. Of course, orthopaedic care is dependent on first-class support from the physiotherapist. Fortunately, in less resourced parts of the world the provision of skilled personnel is sometimes better than in the so-called 'developed' world because of the relatively lower salaries paid. As a consequence, as a generation of children grow up on prophylaxis, healthcare professionals will have much to learn from their more experienced counterparts in less resourced countries.

The patient with haemophilia presents a particular challenge for those providing musculoskeletal care: quality of life can be transformed by such care. We all hope that there is a generation of children with haemophilia growing up who will not have musculoskeletal problems – but until then, this wide-ranging book will provide a useful reference for the comprehensive care team.

E.C. Rodriguez-Merchan
N.J. Goddard
C.A. Lee
Editors

Haemostasis

CHAPTER 1

The Diagnosis and Management of Inherited Bleeding Disorders

B WHITE AND C A LEE

INTRODUCTION

The haemostatic response to vessel injury involves vasoconstriction, the generation of a platelet plug, activation of the coagulation cascade resulting in fibrin clot formation and clot lysis (fibrinolysis). Platelets adhere to the site of vessel injury by interactions between platelet membrane glycoproteins and components of the subendothelium such as collagen and adhesive proteins including von Willebrand factor (VWF) and fibronectin. Platelets are then activated by a variety of agonists at the site of vessel injury resulting in shape change, aggregation, release of secretory granules and the expression of a procoagulant phospholipid surface which provides an ideal bed on which the coagulation cascade is activated. Tissue factor (TF) is expressed at the site of vessel injury and binds to and activates factor VII (FVII) leading to the generation of TF:FVIIa. This complex is critical in the initiation of the coagulation cascade *in vivo* and activates FX either directly or via FIX activation. Activated FX (FXa) converts prothrombin to thrombin, which in turn cleaves fibrinogen to fibrin. Factor XIII cross-links fibrin to produce an insoluble fibrin clot. Factors V and VIII are essential cofactors in the activation of FX and prothrombin, respectively. The final component of the haemostatic response involves clot lysis which is mediated by the fibrinolytic system. Plasmin is produced by the action of urokinase or tissue plasminogen activator on plasminogen and cleaves fibrin, leading to the dissolution of the clot (Fig. 1.1).

Inherited disorders have been described in all aspects of the haemostatic response and these abnormalities can be detected by appropriate laboratory investigations (Table 1.1). Severe deficiency of factors VIII, IX and X are frequently associated with recurrent spontaneous musculoskeletal bleeding which may lead to severe haemophilic arthropathy. FVIII (haemophilia A) and FIX (haemophilia B) deficiency are by far the commonest of these bleeding disorders, and therefore these patients are most likely to attend for orthopaedic review either at the time of diagnosis or for the management of chronic joint disease. Qualitative or quantitative defects in platelets or VWF result in primary mucocutaneous bleeding including epistaxis, gum bleeding and menorrhagia,

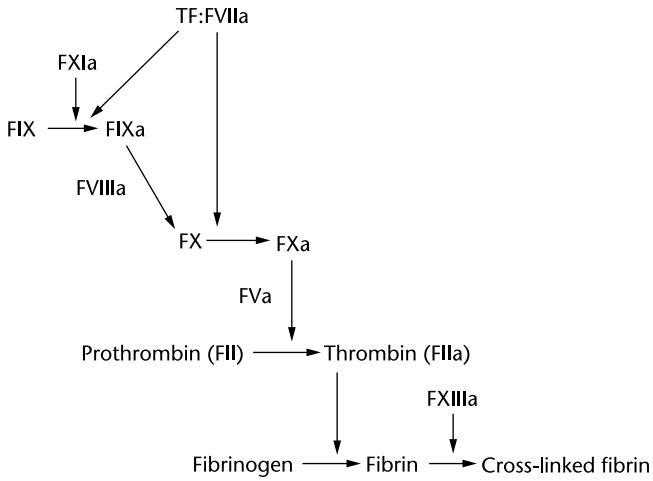

Fig. 1.1 Simplified overview of the coagulation cascade. The key events in the coagulation cascade that lead to fibrin clot formation are illustrated in this diagram. The generation of thrombin plays a critical role in this process and activates platelets, FV, FVIII, FXIII and FXI in addition to cleaving fibrinogen to fibrin. The activated form of each clotting factor is denoted by the letter 'a' (TF = tissue factor).

Table 1.1 Appropriate laboratory investigations to detect inherited bleeding disorders and their common clinical features and haemostatic support.

	Laboratory investigations	Common clinical features	Haemostatic support
Factor VIII or IX deficiency	Prolonged APTT	Musculoskeletal, genitourinary, gastrointestinal bleeding	FVIII or FIX concentrate DDAVP (mild FVIII deficiency) Tranexamic acid
Quantitative platelet defect	Full blood count	Epistaxis, mouth bleeding, skin bleeding, menorrhagia	Platelet transfusion
Qualitative platelet defect	Prolonged skin bleeding time Abnormal PFA-100™ Abnormal platelet function tests	Epistaxis, mouth bleeding, skin bleeding, menorrhagia, gastrointestinal bleeding	DDAVP, platelet transfusion Tranexamic acid
von Willebrand's disease	Prolonged skin bleeding time Abnormal PFA-100™ Reduced VWF (functional and antigen assay) Reduced FVIII	Epistaxis, mouth bleeding, skin bleeding, menorrhagia, gastrointestinal bleeding	DDAVP Tranexamic acid VWF containing concentrate Purified VWF concentrate

PFA-100™ = platelet function analyser. This commercially available machine assesses platelet and VWF function. APTT = activated partial prothrombin time. DDAVP = desmopressin. VWF = von Willebrand factor.

however, with the exception of a severe variant of von Willebrand's disease (VWD), these bleeding disorders do not result in spontaneous musculoskeletal bleeding. In this chapter, we will review the principles of management of inherited bleeding disorders with particular reference to the management of patients with severe haemophilia A and B who require surgery.

TREATMENT OPTIONS FOR INHERITED BLEEDING DISORDERS

The treatment of inherited bleeding disorders requires the correction of

the coagulation defect. Treatment options include factor concentrates, plasma, platelets or desmopressin (DDAVP). In addition, systemic or topical tranexamic acid (which promotes clot stability by inhibiting fibrinolysis) may be used alone or in combination with other treatments.

Factor concentrate

The provision of factor VIII or IX replacement for haemophilia has evolved since the late 1960s from the use of cryoprecipitate and plasma to the development of recombinant FVIII and FIX concentrates. Factor concentrates are prepared from plasma which has been collected from several thousand donors, separated into different fractions and purified using a variety of techniques, including chromatography. The availability of factor concentrate had a major beneficial impact on the morbidity and mortality of haemophilia. However, the enthusiasm associated with the advent of highly effective therapy was soon tempered by the catastrophic outbreak of HIV and hepatitis C infection in the haemophilia population due to the contamination of factor concentrates [1–6]. Appropriate safeguards are now in place to prevent infection, including polymerase chain reaction (PCR) testing of donor plasma and the incorporation of validated viral inactivation steps in the purification process. Current plasma derived factor concentrate is safe, however, the risk of viral infection remains due to the failure of the viral inactivation process to destroy non-enveloped viruses such as hepatitis A and parvovirus B19 and the risk from as yet unidentified infectious agents [7,8].

Recent concerns have focused on the possibility of infection from plasma derived concentrates contaminated with new variant Creutzfeldt–Jakob disease (nvCJD). It is likely that this disease represents the human form of bovine sclerosing encephalitis (BSE) which infected a large number of cattle, especially in the United Kingdom, in the 1980s and early 1990s. There are insufficient data to accurately assess the risk to the haemophilic population. The risk is likely to be low since nvCJD has never been shown to develop as a result of transfusion of blood products either in clinical practice or in animal models [9]. However, nvCJD has been demonstrated in the plasma of infected patients and is unlikely to be destroyed by current viral inactivation processes. Furthermore, there is no effective screening test. As a result, plasma collected from donors in Britain is not currently used for the production of factor concentrates.

The risk of infection from plasma products provided the impetus for the development of recombinant factor concentrates. These products are produced by transfecting animal cells *in vitro* with FVIII or FIX cDNA. Some FVIII products are formulated with human albumin. Despite the potential for viral infection of animal cells and the risks associated with the addition of human albumin, recombinant products are recognized as being the safest available treatment option for patients who require factor replacement therapy. When the use of recombinant products is restricted by local financial constraints, children, women of child-bearing age and previously untreated adults usually receive priority.

Clotting factor concentrates may be administered on demand (that is, at time of bleeding episode) or as prophylaxis (that is, to prevent

bleeding episodes). The dose of coagulation factor is determined by the following equation:

$$\text{Dose of factor concentrate} = \frac{\text{Desired rise} \times \text{weight in kg}}{\text{K}}$$

The K value is assigned to each factor concentrate and reflects the half-life and recovery of the product. The site and severity of bleeding determine the desired rise and frequency of administration.

Primary prophylaxis refers to the treatment of young children with the aim of preventing spontaneous musculoskeletal bleeding and ultimately chronic haemophilic arthropathy. This usually involves the administration of 25–35 IU/kg of FVIII (thrice weekly) or FIX (twice weekly). The less frequent administration of FIX reflects its longer half-life. The aim of this treatment strategy is to maintain the patient's coagulation factor above levels sufficient to prevent spontaneous bleeding. There is considerable clinical evidence that primary prophylaxis results in a dramatic decrease in the spontaneous haemarthrosis and subsequent arthropathy [10]. Secondary prophylaxis refers to the prevention of bleeding episodes in patients with established joint disease. This approach is also appropriate for the prevention of bleeding during the rehabilitation period following joint replacement.

Factor concentrate is usually reconstituted and administered as a bolus dose. However, the use of continuous infusion may be more appropriate for patients who require high-intensity factor replacement at the time of surgery or for severe bleeding complications. This method of administration avoids the peaks and troughs of bolus dosing, allows an accurate measurement of steady levels and is associated with a significant reduction in product requirement [11,12].

A specific problem arises in the treatment of haemophilic patients who have developed inhibitors to FVIII or FIX. These inhibitors are immunoglobulin-G (IgG) antibodies and bind to endogenous or exogenous FVIII or FIX and neutralize its procoagulant function. Approximately 20% of patients with severe FVIII deficiency develop inhibitors, although this complication is rare in FIX deficiency [13,14]. Patients with low responding FVIII inhibitors can be treated with large doses of factor replacement therapy or porcine FVIII, however patients with high responding inhibitors need specific inhibitory bypassing agents such as recombinant factor VIIa or prothrombin complexes [15]. Recombinant VIIa is highly effective in the presence of FVIII or FIX inhibitors. However, adequate levels are not achieved in a small percentage of patients who have a suboptimal clinical response [16].

Desmopressin (DDAVP) is a synthetic analogue of the pituitary hormone antidiuretic hormone. It can be administered by subcutaneous, intravenous or intranasal routes and results in the release of endogenous FVIII and VWF and may also correct a variety of platelet defects. It is used in responsive patients with mild FVIII deficiency, VWD and platelet function defects [17]. The response to DDAVP is not predictable, and therefore patients should undergo a DDAVP trial at diagnosis or prior to surgical procedures [17]. It is contraindicated in children less than one year old because of the risk of hyponatraemia, and in adults with ischaemic heart disease because of the risk of arterial thrombosis.

While DDAVP is a useful alternative to factor concentrate, it is not effective in FIX deficiency or severe FVIII deficiency. In addition DDAVP is not universally accepted as an effective treatment for responsive patients who require major surgery. As a result DDAVP is rarely used as haemostatic cover for major orthopaedic procedures.

There is no specific concentrate available for patients with FV or FX deficiency. A factor concentrate which contains a combination of clotting factors including FX is used for patients with FX deficiency, while fresh frozen plasma is used for the management of patients with FV deficiency. Platelet transfusions may be used for patients with platelet function defects and may occasionally be used as a source of platelet VWF in VWD. Platelet transfusions should be used sparingly in Bernard–Soulier syndrome and Glanzmann's thrombasthenia because of the risk of platelet antibody formation which would render the patient refractory to subsequent platelet transfusions.

SURGICAL MANAGEMENT

Preoperative assessment

Surgery should only be undertaken in centres which can provide continuous access to medical, nursing and laboratory coagulation expertise throughout the patient's hospital stay. The preoperative assessment of patients by the haemophilia service should include the following.

- *Definition of the nature and severity of the bleeding disorder.*
- *Investigation for the presence of an inhibitor and documentation of prior inhibitor formation*. Surgery in patients with inhibitors to FVIII or FIX is hazardous and those patients with high responding inhibitors should only undergo surgery as a matter of absolute necessity. The decision to proceed with surgery should only be made when the surgeon and patient are fully aware that, despite current treatment options with inhibitor bypassing agents, adequate haemostasis may not be achieved in a small number of patients.
- *Confirmation of the immunity to hepatitis A and B*. The immune status of patients is usually assessed on a yearly basis and vaccinations administered accordingly. The purpose of vaccination is to protect patients from viral infection secondary to contaminated red cell transfusions or plasma derived concentrates [18].
- *Documentation as to whether patients are infected with HIV, hepatitis B or hepatitis C*. Surgical, anaesthetic and nursing staff should be aware of the viral status of patients. It is important to identify additional risk factors for bleeding associated with infection (for example, thrombocytopenia or liver dysfunction) or antiviral therapy (protease inhibitors). Protease inhibitors are an integral component of current anti-retroviral treatment strategies. These agents are associated with an increased risk of spontaneous and surgery-related bleeding complications [19]. As a result, we discontinue protease inhibitors for 48 hours prior to major orthopaedic surgery and for approximately 1 week postoperatively. A treatment strategy to correct all other additional risk factors for bleeding complications should be formulated prior to surgery.

• *Liaison with surgical, anaesthetic and nursing staff regarding postoperative analgesia*. Intramuscular injections are contraindicated because of the risk of intramuscular bleeding. In addition, nonsteroidal anti-inflammatory agents should be avoided because of the risk of gastric erosion and platelet dysfunction. Spinal or epidural analgesia can be undertaken provided the postinfusion factor levels are within the required therapeutic range and there are no additional risk factors for bleeding such as inhibitors, thrombocytopenia or concomitant protease inhibitor use.
• *Documentation of management plan*. A treatment strategy should be selected for each patient and should be available to the medical and nursing personnel who will be responsible for patient care. Adequate stocks of factor concentrate should be available to cover surgery and the postoperative period.

Operative care

Patients are usually admitted the day prior to major surgery or on the day of surgery in a similar manner to patients without haemophilia. Blood is crossmatched according to the normal surgical blood-ordering policy of the hospital. Additional units may need to be crossmatched for patients with additional risk factors for bleeding.

A bolus of factor concentrate is administered 1 hour prior to surgery. If it has been decided to administer factor concentrate by a continuous infusion, then this should be commenced preoperatively. It is important to confirm that the postinfusion factor level is within the required therapeutic range *prior* to commencing surgery.

Postoperative care

The postoperative management of patients varies depending on the type of surgery and the practice of each haemophilia centre. We use a continuous infusion for 7 days after major surgery and aim to maintain factor levels at 100 IU/dL during this period.

Thereafter, we treat daily and then on alternate days until day 14 postoperatively [20]. However, there is considerable variation among haemophilia centres in the surgical management of these patients. Some authors recommend a continuous infusion with the aim of maintaining FVIII or FIX levels of 50 IU/dL on the day of surgery, reducing to 30 IU/dL thereafter [21]. There is currently insufficient evidence to justify one approach over the other and current practice reflects the experience of individual centres. Factor concentrate should be administered prior to physiotherapy and removal of stitches, in order to provide optimal haemostasis at the time of greatest risk of bleeding. Furthermore, the administration of prophylactic FVIII (thrice weekly) or FIX (twice weekly) after joint replacement allows the patient to undergo similar rehabilitation programmes to non-haemophilic patients without additional bleeding complications.

ORTHOPAEDIC SURGERY AND UNDIAGNOSED HAEMOPHILIA

Orthopaedic surgeons may be asked to review patients with undiagnosed haemophilia who present with unexplained joint swelling or pain due to haemarthrosis. In this situation, an invasive procedure without coagulation support will result in further joint bleeding and morbidity. Therefore, surgeons should be alert to the possibility of haemophilia in children who present for orthopaedic review and should always perform a basic coagulation screen of activated partial prothrombin time (APPT) and prothrombin time (PT) prior to surgery. This screen should detect the vast majority of bleeding disorders associated with spontaneous haemarthrosis. Orthopaedic patients with a bleeding history should be referred to a haematology or specialist coagulation unit. While many of these patients will not have a defect associated with spontaneous musculoskeletal bleeding, haemostatic support may be required at the time of surgery.

SUMMARY

Severe FVIII and FIX deficiency are the commonest bleeding disorders associated with spontaneous haemarthrosis and subsequent joint disease. The vast majority of other inherited bleeding states are not associated with spontaneous musculoskeletal bleeding but will require coagulation review prior to orthopaedic procedures.

Surgery can be safely performed in patients with severe inherited coagulation disorders provided the coagulation defect can be corrected with replacement therapy. The presence of high responding inhibitors to FVIII or FIX poses a considerable therapeutic challenge and requires the use of inhibitor-bypassing agents such as recombinant FVIIa. While these therapies are usually highly effective, adequate haemostasis cannot always be guaranteed, and invasive procedures should only be performed as a matter of absolute necessity.

It is imperative that surgery is only performed on patients with inherited bleeding disorders in centres that can provide comprehensive coagulation support. Unfortunately, this cannot always be achieved in poorly resourced countries, and this is likely to lead to an increased risk of surgical morbidity and mortality. Thus, the major challenge of the twenty-first century in haemophilia is to provide the resources and training so that these basic principles of haemophilia care can be applied to all patients worldwide.

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Orthopaedic Surgery

CHAPTER 2

General Principles in Orthopaedic Surgery of Haemophilia

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INTRODUCTION

The successful outcome of surgery in haemophilia depends upon a close working relationship between the orthopaedic surgeon and the haematologist. This chapter outlines the general principles involved in undertaking surgery in patients with haemophilia, the surgical technique, preoperative evaluation, the risk of infection after surgery in the HIV-positive patient and the risk of intraoperative transmission of blood-borne diseases.

PREOPERATIVE EVALUATION AND SURGICAL TECHNIQUE

Elective surgery for patients with haemophilia is now possible due to the increasing availability of factor concentrate. Prior to undertaking surgery it is important to establish the exact nature of the haemorrhagic disorder. It goes without saying that the bleeding disorder must be fully corrected before beginning surgery.

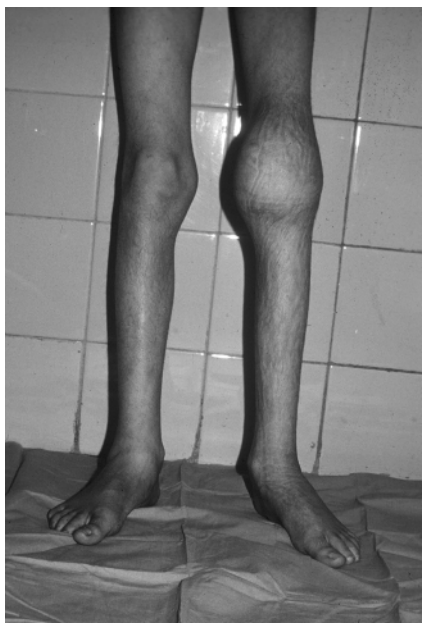

Fig. 2.1 Severe chronic haemophilic synovitis in a young person with haemophilia.

INDICATIONS FOR ORTHOPAEDIC SURGERY

The common indications for orthopaedic intervention surgery in patients with haemophilia have been outlined by Canale [1] and include the following:

- Chronic haemophilic synovitis (Fig. 2.1) that cannot be controlled by adequate factor replacement (synovectomies).
- Severe soft-tissue contractures that have been unresponsive to standard non-operative measures (tendon release, capsulotomy or osteotomy).
- Bony deformities that merit corrective osteotomy.
- A pseudotumour that may require surgical excision and perhaps grafting.
- Severe degenerative change in a joint with increasing disability and incapacitating pain (total joint replacement or arthroplasty).

Post and Telfer [2] emphasized that the surgery must be carried out carefully, with particular attention paid to haemostasis. It has been pro-