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CASE REPORT

Case studies: orthopaedic surgery in adult patients with haemophilia A with inhibitors

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Summary. Whilst orthopaedic surgery in haemophilia patients without inhibitors is now relatively common in specialized centres, until recently there have been only a few sporadic instances of surgery having been undertaken on patients with inhibitors. The availability of recombinant activated factor VII (rFVIIa) for haemostatic cover during surgery allows procedures to be performed that previously may not have been considered possible. Complications associated with thrombosis are rare in haemophilia patients with inhibitors, but bleeding complications remain a concern. Globally, experience of performing orthopaedic surgery in these patients is increasing and many successful outcomes have been reported. However, more knowledge relating to the incidence and type of bleeding complications liable to be encountered, together with further information about appropriate rescue treatment, would be valuable. Data relating to long-term follow-up after surgery would be useful, as would a comparison of outcomes between haemophilia patients with and without inhibitors. Optimal dosing regimens for rFVIIa as surgical cover are still to be determined and further information is required relating to the cost effectiveness of rFVIIa in surgery. Further study should address these issues.

Keywords: arthropathy, haemophilia, haemostasis, inhibitors, orthopaedic surgery, recombinant activated factor VII

1. **The availability of recombinant activated factor VII (rFVIIa) for haemostatic cover during surgery...**
Anchor Name: rFVIIa for haemostatic cover during surgery *[Agency FCB Halesway Olga Kooi]*

Introduction

Orthopaedic surgery in patients with haemophilia and inhibitory antibodies (inhibitors) to factor VIII (FVIII) or factor IX (FIX) concentrates is a challenging clinical event, which in worst-case scenarios can result in loss of life or limb. In our centre, communication in an open-forum setting between patients who have undergone orthopaedic surgery and those seeking similar procedures, together with effective patient-to-clinician communication, is critical to effective treatment. This is also a useful method of providing patients with information based on actual experience.

Major surgical intervention is a relatively new phenomenon in patients with haemophilia and inhibitors. Orthopaedic surgery is most often performed on ankles, knees, shoulders and elbow joints, while hip replacement is less frequent. Surgical options available to orthopaedic surgeons include debridement of the joint, which delays but does not necessarily avoid the need for further major surgery, synoviorthesis, synovectomy, osteotomy, arthrodesis and arthroplasty.

The primary goal of orthopaedic surgery is to relieve chronic pain caused by severe arthropathy. In addition, successful surgery is liable to improve a patient's quality of life and self-esteem as a consequence of restoring joint function, mobility and independence. Surgery also benefits the patient by reducing bleed frequency and subsequent joint damage. In addition, the outcomes and some objective data can be assessed by using one of the various scoring systems available to us (Table 1).

Inhibitor development

According to UK data, the proportion of patients with haemophilia A who develop antibodies to FVIII concentrates has remained constant at around 6% since 1969 [9,10], despite significant changes in the purity of factor concentrates. However, patients with

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Table 1. Surgical outcome scoring systems

Scoring system	
Hospital for Special Surgery (HSS)/Knee Society Score (KSS) [1]	The KSS rates the joint, to give a knee score, and also rates the patient's ability to walk and climb stairs, to produce a functional score. Maximum scores (best outcomes) for both ratings are 100 points.
Harris Hip Society (HHS) [2]	This 100-point scale assesses the hip, with the emphasis on pain and functional capacity. Higher scores indicate better outcomes.
Constant [3]	The Constant score assesses the shoulder. The maximum score (best outcome) is 100 points, 25 of which are related to muscle strength as determined by a patient's ability to lift 25 pounds.
Western Ontario and MacMaster (WOMAC^{TM}) Index [4]	This is a self-administered questionnaire assessing 3 domains (pain [maximum 20 points], joint stiffness [maximum 8 points] and clinical function [maximum 68 points]) in knee and hip osteoarthritis. Lower scores are indicative of better outcomes.
Oxford questionnaire [5–7]	This questionnaire comprises 12 questions, with 5 points being available for each. The worst score that can be obtained is 60 points and the best score is 12 points. Versions of the questionnaire are available for assessing hip, knee and shoulder surgery.
World Federation of Hemophilia (WFH) [8]	The clinical and radiological classification of the Orthopedic Advisory Committee of the WFH assesses haemophilic joints in terms of pain, bleeding, clinical features and radiographic changes. The minimum score (normal joint) is 0, and the maximum score is 25.

lower indigenous FVIII levels (i.e. severe haemophilia) are at higher risk of inhibitor development – the database of the UK Haemophilia Centre Doctors' Organisation (UKHCDO) reports that by 1996 12.7% of patients with severe haemophilia A had developed antibodies to FVIII [9]. More recently, Rodriguez-Merchan *et al.* [11] have reported that inhibitors are present in between 10% and 30% of patients with severe haemophilia A.

A variety of factors may influence the development of inhibitors to FVIII; these can be either patient- or therapy-related (Table 2). Genetic factors can affect the risk of inhibitor formation. Differing risks of inhibitor formation are associated with at least 10 distinct classes of mutations, with the FVIII gene and immune response genes being implicated here [12]. Patients in whom molecular defects are more severe and who lack endogenous synthesis of FVIII may have a prevalence of inhibitors up to 10 times higher than patients who have milder molecular defects [12]. The way in which a patient is treated may also influence the risk of inhibitor development. There has been speculation as to whether ultrapurified products may result in a higher incidence of inhibitors [14]. Reviewing results from a variety of sources, Wight and Paisley [20] reported that in studies in which patients with haemophilia A received more than one concentrate, the cumulative risk of developing a high-responding inhibitor varied between 19.2% and 26.4% (weighted mean 21.9%). In patients treated with a single plasma-derived product the cumulative risk for high-responding inhibitors was between 0% and 2.5% (weighted mean 1.4%); the corresponding values for patients who received a single recombinant product were 11.3% and 18% (weighted mean 15.1%) [20].

Table 2. Factors influencing the development of inhibitors to FVIII in haemophilia patients

Patient-related factors
Molecular defect (e.g. FVIII gene mutations) [12]
Immunological response characteristics (e.g. possible influence of HLA [human leukocyte antigen] genotype) [13]
Other immunological challenges at the time of FVIII infusion (e.g. interferon) [14]
Ethnicity [15]
Family history of inhibitors [16]
Treatment-related factors
Type of FVIII product (e.g. purity as well as viral inactivation method) [17,18]
Product exposure: number of exposures; pattern of exposure; effects of cumulative exposure [19]
Effects of exposure to several different products [20]

Haemophilia patients with inhibitors: treatment

Acute bleeds in haemophilia patients with inhibitors can be managed with a number of agents including prothrombin complex concentrates (PCCs); activated

PCCs (aPCCs) such as Autoplex (Baxter Healthcare Corporation, Glendale, CA, USA) and FEIBA™ (Baxter Corporation, Mississauga, Ontario, Canada); high-dose human/porcine FVIII/IX; and recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark). Long-term inhibitor eradication may be possible using immune tolerance induction, but this procedure requires prolonged administration of high-dose FVIII or FIX and is therefore expensive. In addition, there is a 20% failure rate [21] and a risk of adverse events.

Haemophilia patients with inhibitors: orthopaedic surgery

Because of the potential for life-threatening bleeds and thrombotic adverse events, surgical intervention in patients with haemophilia and inhibitors was rarely performed before the advent of rFVIIa. In a letter to *The Lancet*, Hedner *et al.* [22] reported the first open knee joint synovectomy in an inhibitor patient using rFVIIa and tranexamic acid as surgical cover. No tourniquet was used in this pioneering event. The patient, a 31-year-old male, had high-responding inhibitors. Local fibrin glue and general anti-fibrinolytic drugs achieved haemostasis without electrocoagulation. No abnormal bleeding was apparent and there were no adverse events. Recombinant FVIIa was given at a dose of 54 μg kg^{-1} immediately before the operation, 2 h later and then at 4-h intervals for 2 days. This was followed by 6-h administration for further 10 days. The authors concluded that rFVIIa was haemostatically active and safe when used to provide cover for this patient during his knee operation.

In 1994, two further reports were published that also described the use of rFVIIa in elective orthopaedic procedures performed in haemophilia patients with inhibitors [23,24]. Subsequently, over 40 cases appeared in the literature describing orthopaedic surgery using only rFVIIa [21,25–29]. The recommended dose of rFVIIa for surgical procedures was 90 μg kg^{-1} every 2 h for 24–28 h, with the dosing interval increasing thereafter. In some of the procedures, rFVIIa was administered using continuous infusion [26,27,29]. Oral antifibrinolytic medication was used in addition to rFVIIa in most cases. Recombinant FVIIa was found to be generally well tolerated. Any bleeding complications that arose tended to be related to the administration of lower doses of the agent [28].

In 2003, Tagariello *et al.* [30] reported the first simultaneous total knee and total hip replacement in a patient with haemophilia A with inhibitors. The patient was 44 years old and had severe haemophiliac arthropathy involving several joints. During the operation, the patient received rFVIIa as a bolus injection. Continuous infusion of rFVIIa was subsequently administered during the postoperative period. Consequently, excessive bleeding was avoided. A total of 8.57 mg kg^{-1} of rFVIIa was given to the patient. Tagariello and colleagues reported this to be less than they had previously used in haemophilia patients with inhibitors who had undergone replacement of single joints [30]. For patients with widespread haemophilic arthropathy, performing multiple surgical procedures during a single operation with rFVIIa haemostatic cover is both important and cost effective. Continuous infusion of rFVIIa facilitated administration of the agent. It also contributed to reducing treatment costs by avoiding peak levels associated with bolus injections.

A series of elective orthopaedic surgical procedures performed on haemophilia patients with inhibitors was also recently described [11]. This involved data collected from nine centres worldwide, in which 51 patients underwent 108 surgical procedures. A total of 88 radiosynoviortheses and 20 major orthopaedic interventions were performed. Outcomes were assessed according to the clinical and radiological classification of the Orthopaedic Advisory Committee of the World Federation of Hemophilia [8]. Joint scores were determined before treatment and at follow-up. A decrease of more than 5 points was regarded as a good result, a decrease of up to 5 points or no change was considered to be a fair result, and any increase in the score was a poor result.

The synoviorthesis group comprised 41 patients who underwent a total of 88 procedures, involving injections in 33 knees, 29 elbows and 26 ankles. In 31 of the 88 synoviortheses, patients were treated with rFVIIa. FEIBA™ was administered on 47 occasions, and other methods of treatment were used in 10 procedures. When rFVIIa was used, this was given at a dose of 150 μg kg^{-1} just before the procedure was performed, with three further doses subsequently being administered at 2-h intervals. The mean age of the patients was 14.3 years (range 5–40 years) and they were followed up for a mean of 6.5 years (range 1–10 years). Good results were obtained for 66 of the procedures; there were 14 fair results and eight poor outcomes. No complications were apparent.

The orthopaedic group comprised 10 patients who underwent 20 operations: six total knee arthroplasties; four bone fracture fixations; two total hip arthroplasties; two pseudotumour removals; and six

other procedures. Eight of these patients (16 procedures) received rFVIIa and two patients (four procedures) were treated with FEIBA^{TM}. When rFVIIa was used, this was administered just before the procedure was performed (mean dose 150 μg kg^{-1}; range 90–200 μg kg^{-1}). Patients to whom rFVIIa was given subsequently received the same dose at 2-h intervals for 24 h, followed by continuous infusion (45 μg kg^{-1} h^{-1}) for a further 3–7 days. The mean age of these patients was 32.5 years (range 27–40 years) and the mean follow-up period was 2.3 years (range 1–5 years). There were 16 good results, one fair result and three poor results. Postoperative bleeding complications occurred on three occasions in patients who had received insufficient doses of rFVIIa.

The results presented by Rodriguez-Merchan *et al.* [11] confirm that elective orthopaedic surgery can be successfully performed on haemophilia patients with inhibitors.

Orthopaedic surgery in haemophilia patients with inhibitors: UK experience

At the Royal Free Hospital (Haemophilia Centre), UK, we have treated 1500 patients with factor-deficiency diseases (41% of these patients had von Willebrand's disease, 24% had been diagnosed with haemophilia A, 24% had factor XI deficiency, 7% had been diagnosed with haemophilia B, and 4% had factor V or factor X deficiency. Of the haemophilia A patients, 120 have severe disease. To date we have performed 78 joint replacements in 51 non-inhibitor patients, comprising 54 knee replacements, 20 hip replacements, three elbow replacements and one shoulder replacement, in addition to other less invasive surgery. In our patient cohort we have only three patients who have inhibitors to FVIII. In this small group we have performed two total knee replacements (one revision) and one radial head excision.

The first case we treated was a 76-year-old woman with acquired inhibitors and rheumatoid arthritis. She had progressive loosening of an Attenborough knee replacement culminating in a periprosthetic fracture (Fig. 1). The operative intervention consisted of a resection of the distal femur and insertion of a massive distal femoral replacement, somewhat akin to tumour surgery (Fig. 2). The procedure was carried out under cover of rFVIIa (90 μg kg^{-1} every 2 h for 48 h) followed by a slowly reducing dosage. She was hospitalized for a total of 3 weeks and was able to regain a limited degree of mobility. There were no postoperative complications.

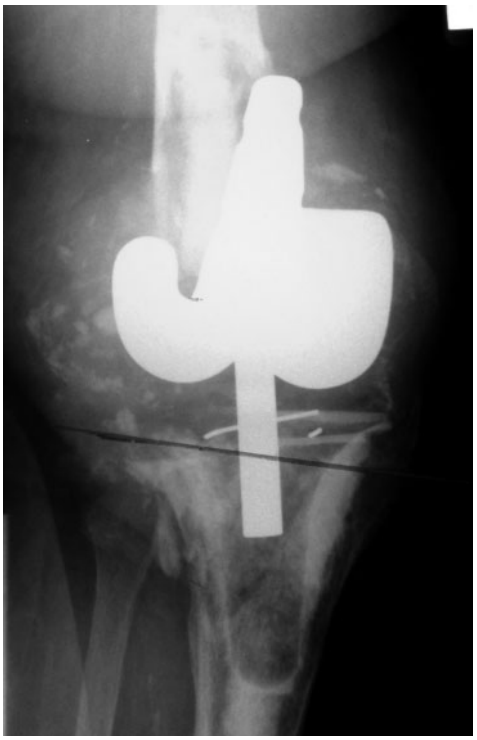

Fig. 1. Preoperative radiograph of revision total knee replacement in a 76-year-old patient with acquired inhibitors. Note the gross loosening of the femoral component, which has eroded through the anterior cortex of the femur.

Our second case was a 31-year-old man who had disease involving both his elbow and right knee. The first intervention was radial head excision, again under cover of rFVIIa (90 μg kg^{-1} every 2 h for 48 h). He was discharged from hospital on the fifth postoperative day with a greatly improved range of motion and reduction in pain. He was re-admitted for elective total knee replacement 6 months later. The operation was carried out using rFVIIa at the same dosage for the first 48 h, reducing to 90 μg kg^{-1} every 3 h on the third postoperative day. There were no immediate postoperative problems, but following the dose reduction on day 3 there was a significant bleeding episode resulting in a painful haemarthrosis. The dose was then increased again to 90 μg kg^{-1} every 2 h for the following 3 days and then reduced. He experienced a further, less severe bleeding episode on day 12 and remained hospitalized for a total of 3 weeks.

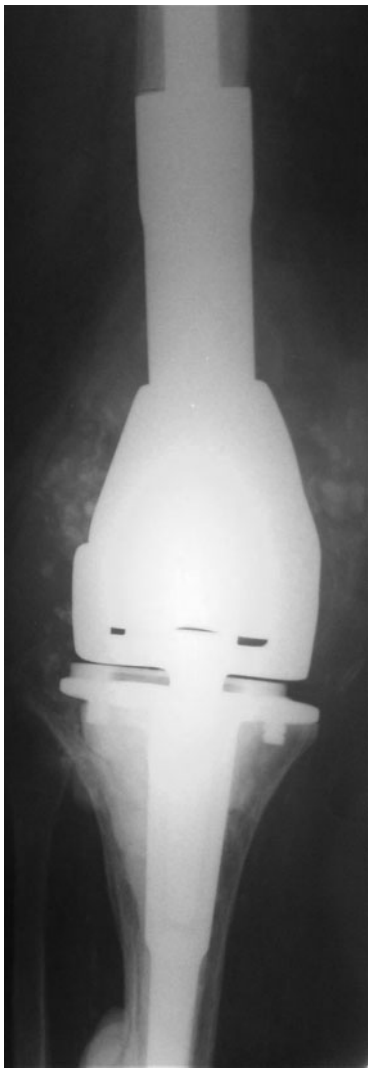

Fig. 2. Postoperative radiograph of revision total knee replacement in a 76-year-old patient with acquired inhibitors. Both components have been removed and the insufficient distal femur has been resected and replaced with a custom-made distal femoral replacement and rotating platform for the tibial component.

We have knowledge of other centres in the UK with experience of performing orthopaedic surgery on patients with inhibitors, including Oxford (where two total knee replacements and one ankle fusion have been carried out), Edinburgh (where hip and knee surgery has been performed), Belfast (one hip surgery), Sheffield, Birmingham, Manchester and Cardiff.

Current situation

The availability of rFVIIa for haemostatic cover has enabled surgery that was previously impossible. Globally, experience of performing orthopaedic surgery in haemophilia patients with inhibitors is increasing. The surgery being performed has become more enterprising and is certainly not for the faint-hearted. Thrombotic complications are rare in inhibitor patients, and surgeons frequently ignore the concept of thromboprophylaxis. However, bleeding complications remain a concern.

As there may be a bias in the literature towards describing positive outcomes, it is likely that failures of treatment are not well-reported and hence pertinent information on how to prevent failures is lacking. More knowledge relating to the incidence and type of bleeding complications liable to be encountered, together with further information about appropriate rescue treatment would be valuable. In addition, data relating to long-term follow-up after surgery would be useful. Optimal dosing regimens for rFVIIa as surgical cover in inhibitor patients are still to be determined. Although 90 μg kg^{-1} of rFVIIa every 2 h has been the standard dose, the consensus of opinion is moving towards higher doses (rFVIIa 120–200 μg kg^{-1}). Discussion is also focused on whether the best means of administering the agent for perisurgical use is by bolus injection or continuous infusion.

More data are needed relating to the cost-effectiveness of rFVIIa in surgery. Recently, a prospective European study, the European Register of Knee Arthroplasty (Eureka), has been set up to look at the costs associated with first-line use of rFVIIa for total knee replacement. This aims to collate retrospective and prospective data, and patients are to be followed for up to 5 years after their surgery. The registry will also permit a comparison of outcomes between haemophilia patients with and without inhibitors.

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