



SURGERY

Surgery in haemophilia patients with inhibitors, with special emphasis on orthopaedics: Madrid experience

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Summary. We report on a series of 92 surgical procedures (90 patients). It includes 35 orthopaedic procedures (33 patients) and 57 non-orthopaedic procedures (57 patients). The orthopaedic procedures include 27 radiosynovectomies (minor surgery) and eight major orthopaedic procedures. The non-orthopaedic procedures include 52 minor interventions and five major procedures. The average age of patients was 34 years (range: 8–56), and the average follow-up time was 3 years (range: 1–6). Of the 92 surgical procedures, 42 were performed with activated prothrombin complex concentrates [factor eight inhibitor bypassing agent (FEIBA)] and 47 with recombinant-activated factor VIIa (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark). Regarding FEIBA treatment in minor surgery, the initial dose was 100 IU kg⁻¹. After 6 h, we continued with 50 IU kg⁻¹ every 12 h for at least 4 days (radiosynovectomies). In minor non-orthopaedic procedures, the dose was continued until day 14. In patients who

underwent surgery with the haemostatic control achieved by means of rFVIIa, the initial dose of rFVIIa in minor procedures (both orthopaedic and non-orthopaedic) was 90–120 µg kg⁻¹. In postoperative days 1–5, the dose was 2–4 × 90–120 µg kg⁻¹ q3–6 h for 24 h. In major procedures (both orthopaedic and non-orthopaedic), the dose was 120 µg kg⁻¹ preoperatively, 120 µg kg⁻¹ q 3 h day 2/day 3–5, and then 90–120 µg kg⁻¹ q 6 h until day 14. There were 87 good results, four fair results and one poor result. Our study has shown that haemophilic patients with inhibitors requiring surgery can undergo orthopaedic and non-orthopaedic procedures with a high expectation of success. In other words, surgery (orthopaedic and non-orthopaedic) is now possible in haemophilia patients with inhibitors, leading to an improved quality of life for these patients.

Keywords: haemophilia, inhibitors, orthopaedics, surgery

Introduction

The development of an inhibitor against factor VIII (FVIII) or factor IX (FIX) is the most common and most serious complication of replacement therapy in patients with haemophilia A or B, resulting from the exclusive use of virus-inactivated, plasma-derived concentrates or recombinant products. Two approaches for the treatment of patients with inhibi-

tors have been proposed. Immune tolerance induction using high-dose FVIII or FIX daily or twice daily for a period of a few months to several years may completely eliminate the inhibitor, again allowing the patient to be treated efficiently with FVIII or FIX [1,2]. However, immune tolerance induction fails in around 20% of cases and is not proposed for all patients because of the high probability of failure or adverse events. Furthermore, this procedure is very costly.

The other possibility is to treat bleeding episodes with prothrombin complex concentrates (PCCs), activated prothrombin complex concentrates (APCCs) such as factor eight inhibitor bypassing agent (FEIBA; Baxter Bioscience, Vienna, Austria) [3–5] or with recombinant-activated factor VIIa

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(rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) [6–9]. In case of failure of APCC or rFVIIa in life- or limb-threatening bleeds or as first-line treatment for major bleeds, high-dose human [10] or porcine FVIII [11] or human FIX may be efficacious if the inhibitor is low or is lowered using plasmapheresis [12] or protein A immunoadsorption [13]. However, the anamnestic rise of the inhibitor will render treatment with FVIII or FIX ineffective within a few days, making the patient resistant to rescue with FVIII or FIX for months or even years.

We report our experience on surgery in haemophilia patients with inhibitors, both in non-orthopaedic and orthopaedic procedures.

Madrid experience

We have performed so far 92 surgical procedures (90 patients), of which 35 were orthopaedic procedures and 57 were non-orthopaedic procedures. The average age was 34 years (range, 8–56) and the average follow-up was 3 years (range, 1–6).

Regarding minor orthopaedic surgery, that is to say radiosynovectomies, 27 joints were treated (intra-articular injections) in 27 patients. Knees were injected with yttrium (^{90}Y), while ankles and elbows were injected with rhenium (^{186}Rh). Twenty radiosynovectomies were performed with APCCs (FEIBA), and seven with rFVIIa (NovoSeven).

With regard to the group of major orthopaedic procedures, six patients underwent eight orthopaedic operations: three total knee arthroplasties (Fig. 1), one total hip arthroplasty (Fig. 2), one fixation of bone fracture, one ankle arthrodesis (Fig. 3), one removal of hardware of the ankle fusion and one knee arthrodesis. In this group, six procedures were performed with rFVIIa (NovoSeven) and two with APCCs (FEIBA). Overall, of the 35 orthopaedic procedures, 22 were performed with FEIBA and 13 with NovoSeven.

Concerning minor non-orthopaedic surgery, 52 patients underwent 52 surgical procedures: 37 central catheter placements, 10 dental extractions, two inguinal hernias, one lipoma, one hydrocele and one cataract. Regarding major non-orthopaedic surgery, five patients underwent five procedures: one thoracotomy (lobectomy), one craniotomy, one pyloroplasty, one appendectomy and one corneal transplant. Overall, of the 57 non-orthopaedic procedures, 23 were performed with FEIBA and 34 with NovoSeven. The data and results of this study are summarized in Tables 1 and 2.

Regarding FEIBA treatment in minor surgery, the initial dose was 100 IU kg^{-1} . After 6 h, we contin-



Fig. 1 (a–c) Total knee arthroplasty in a 27-year-old haemophilia patient with inhibitor and severe haemophilic arthropathy (circle). In the postoperative period, he presented recurrent bleeding because of pseudoaneurysm of a geniculate artery. The complication was satisfactorily resolved by arterial embolization (vascular stent). The final result was fair: (a) Anteroposterior pre-operative radiograph showing a severe degree of arthropathy. (b) Intra-operative view after implantation of the prosthesis and release of the tourniquet. (c) Anteroposterior postoperative view with the prosthesis satisfactorily implanted. Note the vascular stent (metallic device) in the posterior aspect of the joint (arrow).

ued with 50 IU kg^{-1} every 12 h for at least 4 days (radiosynovectomies). In minor non-orthopaedic

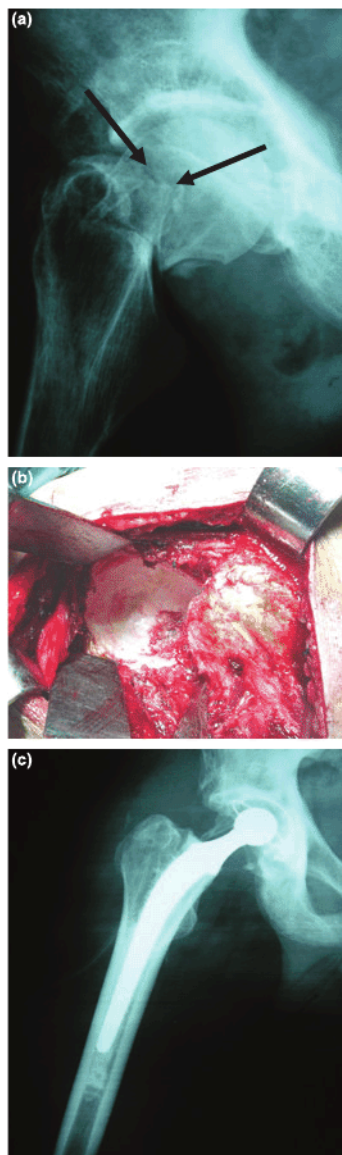


Fig. 2. Total hip arthroplasty in a totally displaced femoral neck fracture of a 53-year-old haemophilia patient with inhibitor and haemophilic arthropathy of the hip: (a) Pre-operative radiograph showing the fracture (arrows). (b) Intra-operative view of the acetabulum showing haemophilic arthropathy. (c) Radiograph after 1 year of the implantation of a cemented prosthesis. The clinical result was good.

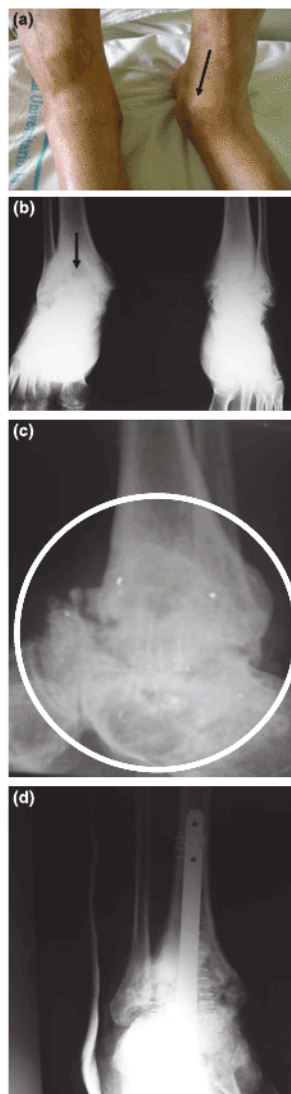


Fig. 3 (a–d) Ankle arthrodesis in a 46-year-old haemophilia patient with inhibitor. It was performed with a retrograde intramedullary nail locked proximally and distally: (a) Clinical view of both ankles. Note the severe deformity of the right ankle (arrow). (b) Pre-operative AP view of both ankles showing a severe degree of arthropathy, mainly in the right ankle (arrow). (c) Pre-operative lateral radiograph of the right ankle showing severe arthropathy (circle). (d) Postoperative radiograph showing the implanted intramedullary nail.

Table 1. Main data and results of orthopaedic procedures (33 haemophilia patients with inhibitors: 27 radiosynovectomies, eight major orthopaedic procedures).

Procedure	No. procedures	Haematological treatment	Result	Complications	Comments
Radiosynovectomies (m)	27	20 with FEIBA, 7 with rFVIIa	19 good, 1 fair	1 postinjection bleeding	Yttrium-90 and Rhenium-186
Total knee arthroplasty (M)	3	2 with FEIBA, 1 with rFVIIa	2 good, 1 fair	1 postoperative bleeding	Required arterial embolization to be resolved
Fixation of femoral neck fracture (M)	1	rFVIIa	Good	None	None
Total hip arthroplasty (M)	1	rFVIIa	Good	None	None
Ankle arthrodesis, removal of hardware (M)	2	2 with FEIBA	Good	None	None
Knee arthrodesis (M)	1	rFVIIa	Good	None	None

M, major procedure; m, minor procedure.

Table 2. Main data and results of non-orthopaedic procedures (57 haemophilia patients with inhibitors: 52 minor procedures, five major procedures).

Procedure	No. procedures	Haematological treatment	Result	Complications	Comments
Central catheter placements (m)	37	17 FEIBA, 20 rFVIIa	All good	None	None
Dental extractions (m)	10	2 FEIBA, 8 rFVIIa	All good	None	None
Lipoma (m)	1	FEIBA	Good	None	None
Hydrocele (m)	1	rFVIIa	Good	None	None
Cataract (m)	1	FEIBA	Good	None	None
Thoracotomy (lobectomy) (M)	1	rFVIIa	Poor	Death (pulmonary complications)	None
Craniotomy (M)	1	rFVIIa	Good	None	None
Pyloroplasty (M)	1	rFVIIa	Good	None	None
Appendectomy (M)	1	FEIBA	Good	None	None
Corneal transplant (M)	1	FEIBA	Good	None	None
Inguinal hernia (m)	2	2 rFVIIa	2 good	None	None

M, major procedure; m, minor procedure.

procedures, the dose was continued until day 14. In patients who underwent surgery with haemostatic control achieved by means of rFVIIa, the initial dose of rFVIIa in minor procedures (both orthopaedic and non-orthopaedic) was 90–120 µg kg⁻¹. During post-operative days 1–5, the dose was 2–4 × 90–120 µg kg⁻¹ q3–6 h for 24 h. In major procedures (both orthopaedic and non-orthopaedic), the dose was 120 µg kg⁻¹ pre-operatively, 120 µg kg⁻¹ q 3 h day 2/day 3–5, and then 90–120 µg kg⁻¹ q 6 h until day 14.

Discussion

Until a decade ago, major surgery in patients with haemophilia and an inhibitor was extremely rare. However, since then, substantial experience has been accumulated regarding adequate haemostatic treatment to cover these patients during any kind of surgery. Surgery requires effective haemostasis to reduce wound haematomas that may ultimately

become infected and jeopardize the long-term outcome. FEIBA and rFVIIa have been used in our series as haemostatic agents, with a high rate of satisfactory results but with one bleeding complication rate after major orthopaedic procedure.

Contemporary surgical and haematological advances (FEIBA, rFVIIa) allow us to perform major operations on haemophilic patients with inhibitors, however, also with a higher risk of bleeding complications than in haemophilic patients without inhibitors [14–16].

Since the introduction of bypassing agents (APCCs, rFVIIa), a substantial number of surgical interventions have been reported without haemostatic problems in haemophiliacs with inhibitors, indicating that the new therapeutic strategies may be effective and safe. Thus, orthopaedic and non-orthopaedic procedures may become routine, which may improve the patients' quality of life. Nevertheless, surgical procedures on inhibitor patients are still difficult in view of the lack of both solid evidence-based dosage

recommendations and routine perisurgical patient drug administration. Although internationally the surgical experience documented with rFVIIa is greater than the one with FEIBA, and rFVIIa was the first agent used by us for major orthopaedic surgery, we have got satisfactory results with both bypassing drugs in all types of surgery (major and minor, orthopaedic and non-orthopaedic).

In conclusion, in our centre, 92 procedures were performed on 90 haemophilic patients with inhibitors with excellent results. Both FEIBA and Novo-Seven helped us to control haemostasis in these patients.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- 1 Brackmann HH, Oldenburg J, Schwaab R. Immune tolerance for the treatment of factor VIII inhibitors. Twenty years "Bonn Protocol". *Vox Sang* 1996; 70(Suppl. 1): 30–5.
- 2 Abildgaard CF, Penner JA, Watson-Williams EJ. Anti-inhibitor coagulant complex (Autoplex) for treatment of factor inhibitors in hemophilia. *Blood* 1980; 56: 978–84.
- 3 Hilgartner MW, Knatterud GL, the Feiba study group. The use of Factor Eight Inhibitor By-passing Activity (Feiba Immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. *Blood* 1983; 61: 36–40.
- 4 Hilgartner M, Aledort L, Andes A, Gill J, the members of the Feiba study group. Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in hemophilia patients. *Transfusion* 1990; 30: 626–30.
- 5 Hedner U, Glazer S, Pintel K *et al.* Successful use of recombinant factor VIIa in a patient with severe haemophilia A during synovectomy. *Lancet* 1988; 2: 1193.
- 6 Hedner U, Glazer S, Falch J. Recombinant activated factor VII in the treatment of bleeding episodes in patients with inherited and acquired bleeding disorders. *Transfus Med Rev* 1993; 7: 78–83.
- 7 Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 1998; 19: 163–76.
- 8 Roberts HR. Clinical experience with activated factor VII: focus on safety. *Blood Coagul Fibrinolysis* 1998; 9(Suppl. 1): S115–8.
- 9 White GC, Taylor RE, Blatt PM, Roberts HR. Treatment with a high titer anti-factor VIII antibody by continuous factor VIII administration: report of a case. *Blood* 1983; 62: 141–5.
- 10 A Multicenter US experience. The use of porcine factor VIII concentrate (HyateC) in the treatment of patients with inhibitor antibodies to factor VIII. *Arch Intern Med* 1989; 149: 1381–5.
- 11 Bona RD, Pasquale DN, Kalish RI, Witter BA. Porcine factor VIII and plasmapheresis in the management of hemophilic patients with inhibitors. *Am J Hematol* 1986; 21: 201–7.
- 12 Lozier JN, Santagostino E, Kasper CK, Teitel JM, Hay CRM. Use of porcine factor VIII for surgical procedures in haemophilia A patients with inhibitors. *Semin Hematol* 1993; 30(Suppl. 1): 10–21.
- 13 Heisel MA, Gomperts ED, Gordon McComb J, Hilgartner M. Use of activated prothrombin complex concentrate over multiple surgical episodes in a hemophilic child with an inhibitor. *J Pediatr* 1983; 102: 951–4.
- 14 Rodriguez-Merchan EC, Wiedel JD, Wallny T *et al.* Elective orthopaedic surgery for inhibitors patients. *Haemophilia* 2003; 9: 625–31.
- 15 Rodriguez-Merchan EC, Quintana M, Jimenez-Yuste V, Hernandez-Navarro F. Orthopaedic surgery for inhibitor patients: a series of 27 procedures (25 patients). *Haemophilia* 2007; 13: 613–9.
- 16 Quintana-Molina M, Martinez-Bahamonde F, Gonzalez-Garcia E *et al.* Surgery in haemophilia patient with inhibitor: 20 years of experience. *Haemophilia* 2004; 10(Suppl. 2): 30–40.