The role of recombinant activated factor VII in the haematological management of elective orthopaedic surgery in haemophilia A patients with inhibitors

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Abstract

The clinical profile and expectations of haemophilic patients with inhibitors have changed over the last three decades, mainly because of the prolongation of life-expectancy, often resulting in an increase of the orthopaedic burden. Recombinant activated factor VII (rFVIIa) is the most frequently used bypassing agent in haemophilia patients with inhibitors during elective orthopaedic surgery. For nearly 30 years, rFVIIa has been successfully used to control haemostasis in several major and minor surgical procedures. Clinical trials, case series, reports and surveys were progressively aimed at optimising rFVIIa usage in very demanding conditions managed in highly specialised centres. Recommendations from consensus opinions and guidelines have been provided on the basis of this clinical experience.

Keywords: haemophilia, inhibitors, recombinant activated factor VII, elective orthopaedic surgery.

Introduction

Haemophilia A and B are X-linked inherited coagulation disorders caused by the deficiency of factor VIII (FVIII) or factor IX (FIX)[1]. Reduced plasma coagulant activity is variably associated with spontaneous bleeding or excessive bleeding after trauma, including surgery[1]. According to the residual activity of FVIII or FIX, haemophilia is classified as mild (6-40%), moderate (1-5%) or severe (<1%). In haemophilia A there is usually a good correlation between FVIII residual activity (FVIII:C) and the severity of the bleeding phenotype[1,2]. Recurrent joint bleeding is the hallmark of the severe form and its occurrence determines the high proportion of orthopaedic operations in all haemophilic patients[3]. The current wide availability of clotting factor concentrates has enabled major orthopaedic surgery to be offered to patients in the last decades as well as the management of the late manifestations of crippling haemophilic arthropathy[2-5].

The development of alloantibodies to administered FVIII or FIX is the major complication of haemophilia treatment[6]. Inhibitors occur in up to 35% of patients with severe haemophilia A, in 3-13% of those with mild/moderate haemophilia A[7,8] and in 1-4% of patients with severe haemophilia B. The pattern of inhibitor development is changing over time and currently around one-third of newly diagnosed inhibitors develop in patients with mild/moderate haemophilia A[5,9].

FVIII inhibitors may arise at any time in a patient's life, occurring at a median of 2 years of age in severe haemophilia and predominantly after the fourth decade in mild haemophilia[7]. Of note, the alloantibodies in the latter can also cross-react with residual endogenous FVIII, shifting a mild-moderate haemophilia into a more severe bleeding phenotype[5]. As more than half of haemophilic subjects have mild/moderate haemophilia, both the clinical and surgical impact of inhibitors are growing[5].

Mechanism of action of recombinant activated factor VII

The conversion of prothrombin to thrombin, which eventually triggers formation of fibrin clots, is driven by factor Xa (FXa) bound to factor Va; the activation of FX by FIXa occurs along the coagulation reaction in the tenase complex, in which FVIIIa displays its action as a mandatory co-factor of FIXa. Recombinant activated factor VII (rFVIIa) bypasses the absence of the anti-haemophilic factors via direct activation of FX at the site of vascular injury[10].

It has always been assumed that rFVIIa primes the extrinsic coagulation pathway by binding tissue factor (TF), a membrane glycoprotein that is exposed on the surface of injured blood vessels[11].

Enhanced thrombin generation by the FVIIa-TF complex not only accelerates fibrin formation, but directly contributes to the haemostatic efficacy of rFVIIa by a number of mechanisms. Thrombin strengthens platelet activation and adhesion to sub-endothelial tissues, improves the stability of the primary clot structure by forming thin fibrin fibres and, finally, activates the inhibition of fibrinolysis[11,12]. The resulting haemostatic plug is more resistant to spontaneous and enzymatic lysis[12].

The relatively high doses of rFVIIa needed to induce adequate thrombin formation depend on the natural competition for TF between endogenous FVII and FVIIa. FVII circulates as an inactive zymogen at levels of ~10 nmol/L, while FVIIa is present in negligible amounts[13]. After infusion of a typical dose

of 90 μg/kg in patients with haemophilia and inhibitors, rFVIIa is able to reach plasma levels of ~20-25 nmol/L, which are sufficient to displace the zymogen FVII from TF[14]. Various experimental assays and models have demonstrated this binding shift, although activation of the zymogen by many other coagulation proteases during the propagation of coagulation to overcome this competition cannot be ruled out[15].

The haemostatic effect of high doses of rFVIIa is explained not only by binding to TF, but also by its uptake in platelets and endothelial cells[11].

The interaction between rFVIIa and platelet phospholipids is relatively weak[16]. Only high doses of rFVIIa are able to generate FXa on activated platelets and to bind to activated platelets, thus providing sustained control of bleeding[11]. However, rFVIIa could be internalised by specific glycoproteins on the platelet surface and stored in platelets for later release at the site of surgical injury[16].

Another ligand of rFVIIa on platelets and, specifically, on endothelial cells is the protein C receptor[11]. The specific interaction could induce three results: first, recruitment of rFVIIa on the surface of endothelial cells activated by injuries[17]; second, the creation of a barrier-protective effect against vascular leakage associated with inflammation and tissue destruction[18]; third, the relocation of rFVIIa over the endothelial layer in extravascular sites, such as joint and bone, to provide adequate haemostasis for a period longer than that of the half-life of the circulating factor[19]. All these effects induce a prolongation of the effective haemostatic action of rFVIIa[16].

A sustained bypassing effect may also be useful for optimal wound healing[11]. A substantial delay in wound healing after haemostatic plug formation was shown in experimental haemophilic conditions[20]. Haemophilia could impair the phases, such as inflammation, proliferation, and remodeling, through which wound healing physiologically progresses[20]. Prolonged bypassing treatment may normalise the wound healing process partially or completely[20].

High-dose and sustained treatment with rFVIIa may be indicated for effective recovery and optimal wound healing following surgical management of haemophilic patients with inhibitors[11,12].

Surgery and blood loss

Good haemostasis is a key determinant of the success of surgery, which is usually distinguished as major and minor according to surgery-related bleeding risk[21]. Controlled surgical bleeding is defined as global intra-operative and post-operative blood loss within 25% of expected for the reference patient (e.g. non-haemophilic patient)[4]. A blood loss over expectation (25-50% and more), the doubling of blood component transfusions and admission to intensive care unit due to bleeding (because of tachycardia, hypotension, etc.) suggest fair to inadequate control of haemostasis[4]. In addition, in patients with inhibitors, poor haemostatic control during surgery is indicated by the use of unplanned additional doses of bypassing agents[4].

Of the numerous types of major surgery, elective orthopaedic surgery (EOS) is the most frequently performed in patients with inhibitors, because of their poor joint status, and requires haemostatic support for periods exceeding 5 consecutive days[21-23]. Minor orthopaedic surgery refers particularly to arthroscopic procedures, frequently required in people with haemophilia[22] , although some people consider these procedures as major in this particular setting.

A European survey conducted in 26 haemophilia centres caring for an average number of 241 patients each (range, 45-613) showed that almost 10% of haemophilia patients undergo surgery: major orthopaedic procedures and liver biopsy are those most frequently performed, alongside an average double number of minor procedures[22]. A relevant proportion of such surgical procedures is performed in patients with inhibitors[24].

Clinical experience

EOS in patients with inhibitors to FVIII or FIX is a major challenge[5]. Although the first surgical procedure performed with rFVIIa treatment dates back 30 years, when a patient with haemophilia and inhibitors underwent a successful synovectomy of the knee in 1988[25], some years later Robert Duthie, an orthopaedic surgeon, stated that the presence of inhibitors was an absolute contraindication to EOS for clinicians and a strong discouragement for patients[26]. This traditional view was based on perceived high risk to achieve and maintain long-lasting adequate haemostasis during surgery in haemophilic patients with inhibitors and has led many surgeons to tolerate greater degrees of orthopaedic morbidity in such patients than in patients without inhibitors[27]. As a consequence, patients with inhibitors have a worse orthopaedic status, with more frequent hospital admissions[28]. The historical position of performing surgery mainly in emergency situations is, therefore, outdated[29]. Patients with inhibitors may have a particularly high requirement for surgery, as reflected by the doubled rate of hospital admissions for orthopaedic or musculoskeletal bleeding and increased procedure rate compared to those for haemophiliacs without inhibitors[28].

Inhibitor patients need more EOS, both minor or major. In published literature, major procedures account for two-thirds of EOS[6] (Table I).

The introduction of rFVIIa has allowed EOS to be performed in a number of haemophilic patients with inhibitors. Greater experience, especially for major surgery, has made rFVIIa the usual first choice in

Table I - Elective orthopaedic surgery (EOS) classified into minor or major procedures[6]. These procedures have been performed with recombinant activated factor VII cover (see references).

Minor EOS	Major EOS
Capsulotomy[30]	Total knee (joint) replacement[33]
Arthrocentesis[6]	Total hip (joint) replacement[34]
Articular drainage[6]	Shoulder joint replacement[35]
Hip debridement[31]	Total hip arthroplasty (cartilage repair)[36]
Knee debridement[31]	Elbow arthroplasty[37]
Achilloplasty[32]	Chemical synovectomy[6]
Femoral angiographic embolisation[6]	Arthroscopic synovectomy[6]#
Calcaneus embolisation[6]	Radiosynovectomy[6]#
	Replacement knee prosthesis[38]
	Reconstruction of a limb[39]
	Knee endoprosthesis[32]
	Osteotomy[6]
	Tenotomy[6]
	Pseudotumour removal[6]
	Knee arthrolysis[32]
	Amputation of the leg[32]
	Bone cyst[40]
	Bone graft[30]
	Osteosynthesis[31]
	Debridement of haematoma[41]

#Considered minor surgery by some authors[6].

EOS, preferred to other bypassing agents (activated prothrombin complex concentrate, aPCC) which are less frequently used in this setting[6]. About 10 years after Duthie's statement, the orthopaedic surgeon Rodriguez-Merchan wrote: "EOS is now possible in haemophilia patients with inhibitors"[42] and that this was mostly due to the increasing use of rFVIIa[43].

At first licensed for the treatment of bleeding episodes in haemophilia patients with inhibitors, rFVIIa (Novoseven® RT; Novo Nordisk A/S, Bagsvaerd, Denmark) was subsequently approved for the prevention of bleeding during surgical interventions or invasive procedures in patients with haemophilia A or B with inhibitors[44,45].

The first 20 years' experience of surgery with recombinant activated factor VII

Among about 50 publications inherent to the first 20 years of use of rFVIIa in the surgical setting reporting over 200 major and minor procedures, at least 25 clinical studies, case series, case studies and reports of registry databases on orthopaedic surgery were published between 1988 to 2007. These papers documented the accumulating experience with rFVIIa on adequate haemostatic coverage during any type of orthopaedic intervention, particularly major EOS[6,44-46]. Globally, rFVIIa was the most used by-passing agent, covering more than 60% of elective orthopaedic procedures[6].

In 1998, Schulman reported on 21 major operations (not only orthopaedic) and 57 minor procedures (mainly non-orthopaedic) in which bolus treatment with rFVIIa was used and judged as excellent or effective in 81% of cases[47].

In the second decade, some key studies assumed an evidence-based role, supporting the haemostatic efficacy of rFVIIa together with an improvement of orthopaedic results (Table II).

The main finding of the first 20 years of surgical experience with rFVIIa was that interventions and procedures previously deemed unfeasible or rarely undertaken in haemophiliacs with inhibitors had become possible. Along with other therapeutic procedures and improvements of medical devices, rFVIIa has contributed to make EOS a reality for these patients[46]. Even patients with high responding inhibitors could finally undergo both EOS and invasive procedures safely with satisfactory results[6].

Key studies

To date, various studies have been conducted with rFVIIa in inhibitor patients undergoing surgical procedures, including randomised trials using different doses of the protein, continuous infusion or comparison of bolus dosing versus continuous infusion, as well as a recent post-marketing surveillance study[55]. Despite the small population of haemophiliacs with inhibitors, these key trials recruited a considerable number of patients.

The first clinical trial was a double-blind, randomised, multicentre, parallel-group, dose-finding study of up to 5 days comparing two doses (35 µg/kg or 90 µg/kg) of rFVIIa in attaining and maintaining effective haemostasis during and after elective surgical procedures, ten of which were defined as EOS[30]. Prior to surgery, treatment success was defined by blood loss rated as expected compared to that of non-haemophilic patients; after surgery, satisfactory haemostasis was rated as success[30]. The dose of 90 µg/kg every 2 hours from incision/intubation for the following 48 hours and every 2 to 6 hours for 3 additional days resulted in successful haemostasis in all EOS patients[40]. This impressive result qualified rFVIIa 90 µg/kg as a first-line choice for elective surgical procedures, particularly major EOS[30] (Table III).

A prospective study was performed with the primary aim to achieve a plasma FVII coagulant activity over 30 IU/mL by continuous infusion in nine patients undergoing total knee replacement[43]. The median age was 40 years (range, 25-76 years)[33]. Haemostasis was judged as effective in eight subjects at the end of surgery, in five subjects 8 hours after wound closure and in all nine patients by 24 hours until the final infusion day[33].

The third study was a multicentre, randomised, parallel-group trial comparing, in an open-label design, bolus infusions with continuous infusion of rFVIIa in patients undergoing 16 major EOS[56]. Of note, there were patients of all ages, up to 67 years[6]. The overall haemostatic efficacy, as subjectively assessed by the

Table II - Representative series during the first 20 years of use of recombinant activated factor VII (rFVIIa) in elective orthopaedic surgery (EOS).

Reference	Number of EOS or relevant procedures	Haemostatic and surgical outcomes
Ingerslev *et al.*, 1996[48]	13 (13 major procedures)*	92% good post-operative haemostasis 92% excellent efficacy score
Scharrer *et al.*, 1999[49]	3 (2 major, 1 minor procedures)	100% good intra-operative and post-operative control of blood loss
Santagostino *et al.*, 2001[50]	10 (10 major procedures)	100% satisfactory haemostasis
Smith MP *et al.*, 2001[51]	6 (6 major procedures)	75% good haemostatic control with continuous infusion (and bolus as needed)
Rodriguez-Merchan *et al.*, 2003[42]	47 (16 major, 31 minor# procedures)	100% good orthopaedic results 15% of bleeding complications in major procedures (three patients treated with insufficient doses of rFVIIa)
Mehta *et al.*, 2004[52]	3 (3 major procedures)	100% good haemostatic and orthopaedic results
Goudemand *et al.*, 2004[43]	7 (7 major procedures)	100% good orthopaedic results (one patient required longer treatment with rFVIIa)
Valentino *et al.*, 2011[45]§	5 (major or minor procedures)	70% effective and partially effective haemostasis
Rodriguez-Merchan *et al.*, 2007[53]	7 (7 major procedures)	86% good haemostatic response (one patient required arterial embolisation)
Croteau *et al.*, 2016[54]‖	23 (23 major procedures)	100% of efficacy in paediatric patients (n=6); 78-87% in adult patients (n=17) at 120 hours

*Life-saving or essential surgery. #The minor procedures were radiosynoviortheses, equally distributed among knees, elbows and ankles. §Data from the Hemophilia Research Society registry for the period 1999-2003. ‖Data from the peri-operative dosing study SURG2 started in 1998.

Table III - Key data from clinical studies on the use of recombinant activated factor VII (rFVIIa) in elective orthopaedic surgery (EOS) in patients with haemophilia A or B and inhibitors.

Reference	N. of EOS	Type of relevant EOS with rFVIIa	Successful haemostatic outcomes
Shapiro *et al.*, 1998[30]	n=10	5 synovectomies 2 hip arthroplasties 1 knee joint manipulation 1 knee cartilage repair 1 femur bone graft	100% intra-operative 100% post-operative (90 µg/kg) 60% post-operative (35 µg/kg, suboptimal dose)
Ludlam *et al.*, 2003[33]	n=9	8 total knee replacements 1 above-knee amputation	89% intra-operative 56% post-operative at 8 hours 100% post-operative at 8 hours (supplemental bolus of rFVIIa) 100% post-operative at 24 hours
Pruthi *et al.*, 2007[56]	n=16	8 knee arthroplasties 4 arthroscopic synovectomies 3 hip arthroplasties 1 arthrotomy, irrigation and debridement	75% for bolus infusion 73% for continuous infusion
Takedani *et al.*, 2015[57]	n=24	11 arthroscopic synovectomies 3 joint replacements 2 shoulder arthroplasties 1 elbow arthroplasties 1 above-knee amputation 6 other EOS	88% intra-operative control 75% post-operative control 92% maintenance of hemostasis

investigators, was similar, being effective in 75% of major or minor procedures until discharge or post-operative day 10[56]. About 50% of patients required supplemental doses of rFVIIa in the intra-operative or post-operative period, without significant differences between groups[56]. As measured by laboratory FVII activity levels during or after surgery, sustained haemostatic levels were achieved[56].

In summary, three prospective trials demonstrated the efficacy of rFVIIa in patients undergoing major EOS and this is a unique evident feature of rFVIIa[24].

A Japanese 10-year post-marketing surveillance study was performed on the haemostatic efficacy of rFVIIa in patients who underwent minor and major surgery, with a predominance of EOS[57]. rFVIIa was administered by bolus injection in two-third of 24 patients with congenital haemophilia A or B with inhibitors[57]. Intra-operative bleeding was rated as controlled if it was less than expected or the same as expected as for haemophilic patients without inhibitors undergoing surgery. Post-operative control until 3 days after the intervention was judged effective if bleeding

was stopped or considerably reduced and, additionally, haemostatic maintenance of the surgical wound until suture removal was observed[57]. The efficacy rate of rFVIIa treatment on bleeding during or post-surgery was high and in line with that of previous reports[57].

The studies by Shapiro *et al*.[30] and Pruthi *et al.*[56] with rFVIIa were the only two trials performed until the end of 2014 and eligible by selection criteria of Cochrane review as randomised controlled trials comparing any treatment for controlling bleeding in people with haemophilia undergoing major and minor surgical interventions[58].

The third decade of surgical experience with recombinant activated factor VII

New reports included large series of planned minor and major orthopaedic interventions in haemophilia patients with inhibitors. Table IV summarises the widest experiences with rFVIIa[32,59-64], although an extensive USA survey is not included due to the lack of published results specifically related to EOS[24]. This last research collected data from 98 haemophilia treatment centres, in which about 300 orthopaedic procedures were performed in the past 10 years[24]. Approximately one third of the operations were designated as major surgery[24]. rFVIIa was used by 83/85 centres, clearly showing that it is the most used bypassing agent in this setting[24].

At the end of the first 20 years of experience in EOS, Caviglia *et al.* collected 206 cases of published surgical procedures covered with rFVIIa, of which 172 were major and 34 were minor procedures[6]. A major contribution to illustrating the clinical efficacy and safety of rFVIIa in orthopaedic surgery is provided by the Japanese post-marketing surveillance data collected from May 2000 to March 2010, recently published by Takedani *et al*[57]. Their report also includes the largest experience with patients with haemophilia B and inhibitors and patients with acquired haemophilia A. Overall, bleeding was stopped or reduced considerably in 34/38 procedures (89%) in patients with congenital haemophilia A and in 10/13 (77%) procedures in patients with haemophilia B. Only a single episode of mild superficial thrombophlebitis, not requiring treatment, was observed.

Finally, apart from haemophilia with inhibitors, surgical haemostasis was achieved with rFVIIa in patients with von Willebrand's disease complicated by alloantibodies (e.g. Boadas *et al.*[31]). Recombinant FVIIa has been recommended as a therapeutic approach for this rare condition[65].

Despite the complicated and invasive nature of EOS, the proportion of procedures covered by rFVIIa with effective haemostasis has been consistently high[6,44]. The most recent studies have been aimed at optimising the efficacy of rFVIIa in EOS in haemophilia patients with inhibitors[57].

Safety of recombinant activated factor VII in elective orthopaedic surgery

The potential thromboembolic risk associated with rFVIIa has been analysed in a number of studies, with a particular focus on approved European indications[66]: bleeding episodes and prevention of bleeding during surgery or invasive procedures in haemophilia A or B patients with inhibitors >5 Bethesda units or in those expected to have an anamnestic response to FVIII or FIX factors, acquired haemophilia, congenital FVII deficiency, and Glanzmann's thromboasthenia refractory to platelet transfusion[67]. The methodology of the pharmacovigilance programmes on off-label use of rFVIIa was criticised, since the safety risk identified outside of licensed indications are specific to particular populations and clinical circumstances[68-70].

A review of published data on rFVIIa until 10 years ago in haemophilia patients with inhibitors indicated that the incidence of thrombotic events associated with its use at a recommended dose (90 µg/kg every 2-3 hours until haemostasis is achieved) was about 4/100,000 infusions[71]. In a very recent safety review, 85 thrombotic events (mainly venous)

Table IV - Representative series during the last 10 years of use of recombinant activated factor VII (rFVIIa).

Reference	Number of EOS or relevant procedures	Haemostatic and surgical outcomes
Giangrande *et al.*, 2009[59]	13 (13 major procedures)	85% good haemostatic control during surgery 92% extremely satisfactory final outcome
Solimeno *et al.*, 2009[60]	7 (7 major procedures)	71% good haemostasis (100% with additional doses)
Balkan *et al.*, 2010[61]	28 (26 minor procedures)	100% good response (17% with additional doses)
Rodriguez-Merchan *et al.*, 2010[62]	13 (6 major procedures)	94% good result
Boadas *et al.*, 2011[31]	12 (8 major procedures)	83% effective haemostasis (92% with an additional dose)
Neufeld *et al.*, 2013[63]	92* (17 EOS estimated)	89% effective and 9% partially effective haemostasis (overall results in HTRS registry**)
Polyanskaya *et al.*, 2012[32]	23 (16 major procedures)	100% effective intra-operative and post-operative haemostasis
Ju *et al.*, 2015[64]	9 (9 major procedures)	67% successful bleeding control

*Values estimated from a graph; **all bleedings (not only surgical) in the Haemophilia and Thrombosis Research Society (HTRS) registry.
EOS: elective orthopaedic surgery.

were reported following an estimated 4 million doses of rFVIIa (90 μg/kg), most used in patients with congenital haemophilia with inhibitors[70]. Most patients (60%) recovered from the arterial or venous thrombosis without any sequelae[70]. In particular, only one thrombotic event (in an arterial-venous fistula) was reported across the clinical trials on haemophiliacs with inhibitors conducted with rFVIIa in the last 10 years[70]. Consequently, the incidence of thrombotic events appears to be decreasing gradually as the experience with the use of rFVIIa increases.

EOS is a well-known primary risk factor for venous thrombosis. In the two randomised clinical trials in a surgical setting performed with rFVIIa, one patient undergoing total knee arthroplasty developed thrombosis in the left popliteal vein and proximal peroneal vein, but he continued to receive rFVIIa without adverse consequences[30]; another patient developed a right internal jugular vein thrombosis[56].

To date, the use of higher rFVIIa doses for surgical prophylactic regimens has not been associated with an increased risk of thrombotic events[70]. A specific review on higher than standard (90 μg/kg) rFVIIa doses, also subsequently administered as it occurs in a surgical setting, did not identify any safety issues, and no thrombotic events were reported in association with over 60,000 doses analysed[70].

These observations are of value when a haemostatic restorative treatment such as rFVIIa removes the protection from venous thromboembolism conferred by the coagulation defect[66,71]. In addition, protective effects are reduced as a patient ages and develops comorbid conditions that predispose to thrombosis[66].

The use of rFVIIa for surgical coverage is not associated with a risk of systemic activation of the coagulation system, because the interaction with TF is localised only at the site of the surgical injury[72]. According to recommendations from experts, mechanical methods of thromboprophylaxis are advised in major EOS with a high thrombotic risk, including that related to a prolonged stay in hospital[73]. In less invasive orthopaedic procedures and in the absence of additional thromboembolic risk factors, early mobilisation is usually sufficient to prevent thromboembolic events[73].

Role of recombinant activated factor VII in the current context of elective orthopaedic surgery

The management of orthopaedic surgery, and in particular total joint replacement, with rFVIIa may be very expensive, requires established skills and it is not widely affordable, especially in small haemophilia care centres. Costs may exceed € 500,000, especially for joint prosthesis for which treatment may last 14 days. In the past, continuous infusion (see below) and concurrent total hip and knee replacements[74] have been successfully carried out to reduce costs[30,33,48]. A recent analysis showed that the use of rFVIIa for surgery in patients with haemophilia and inhibitors could be cost-effective because of a significant reduction of bleeding episodes and improvement of quality of life[75]. However, special policies must be adopted to assure that these procedures are carried out at highly specialised centres to achieve the best results and to minimise the risk of bleeding and of excessive or inadequate treatment.

Based on the above data from now extensive surgical experience with rFVIIa, it is apparent that EOS can be performed confidently in patients with haemophilia and inhibitors. As a whole, the use of rFVIIa in major surgery is greater than that of any other bypassing agent[6,44,62]. During the first 20 years of experience with rFVIIa, major EOS has rarely been reported using aPCC, despite the availability of this product in the same period and even before rFVIIa entered the market[53].

Unlike rFVIIa which is free of other coagulation factors and carries no risk of an anamnestic response[69], plasma-derived aPCC has been associated with an anamnestic rise in antibody titre in up to 30% of cases because of the trace content of FVIII[76].

While there have always been concerns about the optimal dose and duration of aPCC treatment during surgery, with the suggested maximum daily dose of aPCC being around 200 IU/kg[77], there are more safety and efficacy data about treatment with rFVIIa at different doses and modes of administration[42,77].

rFVIIa may be administered by intermittent bolus infusions or by continuous infusion, although the latter is not officially approved. As approved and recommended in guidelines for surgical procedures, an initial dose of rFVIIa is given immediately prior to skin incision and repeated as a bolus injection at 2-hour intervals for the subsequent 48 hours for major procedures (every 2-6 hours for 48 hours in minor interventions), after which the dosing interval is increased to 3-4-6 hours in following days, generally for 2 weeks. (Table V)[27,29,78].

The initial dose of 90 μg/kg was gradually increased to 120 μg/kg and 180 μg/kg following the results of a number of studies, with the aim of optimising the dosing regimen[59].

Although off-label, continuous infusion of rFVIIa may have favourable results in the surgical setting, eliminating peak and trough levels, thus further reducing the thrombotic risk and the overall requirement for rFVIIa. However, the results of studies involving this mode of administration are controversial: in some experiences haemostatic outcomes were comparable to those with bolus injections, in others continuous infusions had better efficacy[33,50,51,56]. The data indicate that, after a pre-operative bolus of 90 μg/kg, rFVIIa infusion at 50 μg/kg/h from intervention until day 5 produces sustained, high continuous plasma

Table V - Recommended dosage of recombinant activated factor VII (rFVIIa) for surgery by bolus injection[29,81].

rFVIIa dose	Pre-operative	First 48 h	Days 3-5	Days 6-8	Days 8-14/discharge
Minor procedure	90-120 µg/kg	90-120 µg/kg q2-6h	90 µg/kg q2-6h	90 µg/kg q2-6h as needed	90 µg/kg q2-6h (or prn)
Major procedure	90-120-180 µg/kg	90-120 µg/kg q2h	90-120 µg/kg q2-4h	90 µg/kg q3-4h	90 µg/kg q4-6h

120 and 180 µg/kg are off-label doses.

procoagulant activity (FVII:C levels) adequate to achieve haemostasis. The infusion is tapered to 25 µg/kg/h in the following days[51,56].

Corroborating this, the maintenance of a proper dose is crucial to avoid re-bleeding in the first 5 days following surgery, until major repair processes in the damaged tissue are complete[27,32].

This practice overcomes the lack of tools to anticipate a patient's dose response to bypassing agents, because of inter-patient and intra-patient variability in the surgical setting of the haemostatic pattern[79,80].

It is well known that usual laboratory tests have a limited role when using by-passing agents since no change of FVIII is obtained. In particular, monitoring FVII level is of a little help and the actual level may not correlate with clinical outcome, although some shortening of the activated partial thromboplastin time may occur in addition to the dramatic shortening of prothrombin time. Other tests have been explored to obtain a reliable marker of clinical outcome. Over 20 years of laboratory research on the thrombin generation assay have not been able to achieve definitive standardisation of the test for predicting the haemostatic efficacy of bypassing agents[80]. Moreover, the thrombin generation assay measures the activity of generated thrombin, but provides limited information on clot stability after surgery, while whole blood thromboelastography is mainly indicative of fibrin clot stabilisation and lysis[80]. Rotational thromboelastometry could play a complementary role to the thrombin generation assay, as recently observed in eight patients undergoing elective surgery, who showed improvements of coagulation parameters to normal levels in the immediate, pre-operative and peri-operative stages of rFVIIa treatment[81].

The difficulties in monitoring the haemostatic efficacy of bypassing agents and predicting clinical outcome highlight the importance of care being provided by a multidisciplinary team of trained professionals.

Comprehensive recommendations are available[6,27,59] and could be summarised by global care delivered in specialised centres with staff (surgeon, anaesthesiologist, haematologist, nurse, social worker, physiotherapist, etc.) experienced in the management of patients with inhibitors and good communication among team members throughout the entire surgical procedure, from extensive pre-surgical evaluation to adequate information for patients and their families[6,27,59].

Conclusions

The effective and safe clinical use of rFVIIa for EOS in haemophilic patients with inhibitors is supported by a nearly 30 years of increasing experience worldwide.

The indications for orthopaedic surgery, namely chronic pain and immobility, are actually the same in these patients as those in patients without inhibitors. However, patients with inhibitors may have a higher risk of undergoing EOS and it is likely that their increased life-expectancy will result in a larger number of patients requiring EOS.

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