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ORIGINAL ARTICLE *Treatment*

Elective surgery in patients with congenital coagulopathies and inhibitors: experience of the National Haemophilia Centre of Venezuela

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Summary. Elective surgery in patients with congenital haemophilia with inhibitors carries a high risk of bleeding. However, inhibitor patients also have a high risk of haemarthroses and other orthopaedic complications, and surgery could improve their quality of life. Successful elective surgery has been reported in inhibitor patients under haemostatic cover with plasma-derived activated prothrombin complex concentrate (pd-aPCC) or recombinant activated factor VII (rFVIIa). Recombinant FVIIa has recently become available in Venezuela and, unlike pd-aPCC, has not been associated with an anamnestic response. The aim of this study was to assess our experience using rFVIIa as a first-line and sustained treatment in elective invasive surgical procedures at the National Haemophilia Centre in Venezuela. Surgical procedures were classified as major or minor, under haemostatic cover with rFVIIa. A total of 13 patients (12 with haemophilia A with high-responding inhibitors and one with von Willebrand's disease type 3) underwent a total of 19 surgical procedures under rFVIIa cover. Thirteen procedures were classified as major surgeries. Intraoperative haemostasis was achieved in the majority of patients. Only two patients required an additional dose of rFVIIa, at 30 min and 75 min, respectively, with good results. Postoperative haemostasis was considered effective in 16 of 18 (89%) of the procedures in haemophilia A patients. Treatment was considered to be ineffective in two patients because of excessive postoperative bleeding. Data from the study provide no safety concerns, and demonstrate that rFVIIa provides effective haemostatic cover in elective surgery in patients with inhibitors; research is ongoing to determine the optimal dose for such procedures.

Keywords: bypassing agents, inhibitors, recombinant FVIIa, surgery

Introduction

The availability of clotting factors and the provision of care by a multidisciplinary team of trained professionals within a comprehensive care setting has made it possible to perform elective surgery in patients with haemophilia; this has been instrumental in improving musculoskeletal function and quality of life in these patients. However, this was not the case for haemophilia patients with inhibitors for whom, historically, surgery was performed only as a life-saving procedure [1] as it was considered difficult, with an untoward risk of bleeding [2]. Inhibitor patients have a higher risk of haemarthroses and other orthopaedic complications than non-inhibitor patients [3,4], which affects their quality of life [5] and increases their susceptibility to complications that require orthopaedic procedures.

Two bypassing agents are used to treat bleeding episodes in haemophilia patients with high responding inhibitors: plasma-derived activated prothrombin complex concentrate [pd-aPCC, Factor Eight Inhibitor Bypassing Agent (FEIBA®); Baxter Healthcare, Vienna, Austria] and recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsværd, Denmark). Both are considered effective in most cases, although individual variability in the response to treatment may be observed [6]. Minor and major surgical procedures performed under haemostatic cover with bypassing agents have a high rate of satisfactory results in patients with high responding inhibitors [7–10], although more published data are available for rFVIIa than pd-aPCC in elective orthopaedic surgery, particularly major surgeries [11,12]. Haemophilia patients with inhibitors should not, therefore, be denied orthopaedic surgery that could enhance their quality of life, solely because of their inhibitor status [13].

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The recent availability of rFVIIa in Venezuela provided the opportunity of performing elective surgery procedures under rFVIIa cover in inhibitor patients attending the national haemophilia reference centre. This article presents our experience using rFVIIa as a first-line and sustained treatment pre-, peri- and post-surgery) in 19 elective invasive procedures performed in 13 patients.

Methods

Patients

Patients with haemophilia or von Willebrand's disease (VWD) type 3 and high-responding inhibitors underwent elective surgery with first-line rFVIIa haemostasis at the National Haemophilia Centre in Venezuela between August 2006 and June 2009. All haemophilia patients had previously responded well to rFVIIa treatment for mild or moderate bleeds.

Preoperative evaluation

Medical evaluation prior to surgery included determination of inhibitor titre, maximum inhibitor peak, type of anamnestic response, comorbidities, vaccinations and serological status. Medications such as non-steroidal anti-inflammatory drugs were avoided.

Surgery

Surgical procedures were classified as minor or major, according to the Committee of Latin America on the Therapeutics of Inhibitor Groups (CLOTTING) Guidelines [14]. Any abdominal and orthopaedic surgery was considered major [15]. Procedures requiring only skin excision or small sutures were considered minor. Among orthopaedic procedures, only synoviorthesis was classified as minor [10].

Haemostatic cover

An initial dose of rFVIIa was given 10 min before skin incision and repeated as a bolus injection every 2 h for 24–48 h, after which the dosing interval was increased. The initial rFVIIa dose used in the majority of patients was 90–120 μg kg^{-1}, as approved and recommended in guidelines [10,13,14]. One patient received rFVIIa 180 μg kg^{-1} based on a case using this dose safely to cover orthopaedic surgery [16]. A further patient received a single 260 μg kg^{-1} dose before undergoing minor procedures, as he had previously responded well to this dose. Recombinant FVIIa was administered for 1–5 days for minor surgery and 6–14 days for major surgery [10].

Results

Thirteen patients [mean ± SD, age: 16.64 ± 9.7 years (range 4–41)] underwent 19 elective invasive procedures (13 major surgeries) (Table 1). Twelve patients had haemophilia A (10 severe) with high-responding inhibitors, and one female patient had VWD type 3 with a deletion of the von Willebrand factor (VWF) gene and a severe inhibitor to VWF that blocked normal platelet ristocetin-induced platelet agglutination [17]. Three of the haemophilia patients underwent two surgical interventions each (patients 1, 6 and 12), and one patient underwent four chemical synoviortheses (patient 13). The mean (±SD) peak inhibitor titre for the haemophilia patients was 76.1 ± 74.7 Bethesda Units (BU) and inhibitor titre prior to surgery varied from 0.5 to 45 BU.

Table 1. Patient characteristics.

Patient	Age (years)	Diagnosis	Maximum inhibitor titre (BU)	Previous inhibitor titre (BU)	Elective surgery procedure	Surgery classification
1	13	Severe HA	155	22	Surgical removal of haemophilic pseudotumour of the jaw	Major
	15	Severe HA	155	24	Drainage of haemophilic pseudotumour of the fifth finger	Major
2	27	Severe HA	66	45	Inguinal hernioplasty and surgical removal of epididymal cyst	Major
3	20	Severe HA	13	1	Achillotenotomy	Major
4	21	Severe HA	67	7	Percutaneous aspiration of pseudotumour in shoulder and resection of ear granuloma	Major
5	9	Severe HA	80	1	Surgical reduction of a femur fracture	Major
6	4	Moderate HA	106	15	Debridement of necrotic wound in finger	Major
					Amputation of first phalanx of finger	Major
7	18	Severe HA	16	0.5	Moore osteotomy	Major
8	41	VWD type 3	Strong VWF inhibitor	–	Resection of anal fistula	Major
9	13	Severe HA	15	8.6	Arthroscopic synovectomy of the knee	Major
10	21	Moderate HA	32	0.9	Achillotenotomy	Major
11	19	Severe HA	256	4	Hip and knee debridement	Major
12	8	Severe HA	10	4.2	Implantation of ureteral catheter	Minor
					Cytoscopy and removal of ureteral catheter	Minor
13	4	Severe HA	18	8	Chemical synoviorthesis (four procedures)	Minor

BU, Bethesda units; HA, haemophilia A; VWD, von Willebrand's disease; VWF, von Willebrand factor.

1. **This article presents our experience using rFVIIa as a first-line and sustained treatment pre-, peri...**
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Table 2 summarizes the haemostatic treatments for each surgical procedure. The mean (±SD) initial bolus dose of rFVIIa was 145.4 ± 66.7 μg kg^{-1}, the mean total dose was 157.2 ± 168 mg and a mean of 33.1 ± 27.6 rFVIIa doses were administered. Intraoperative haemostasis was achieved during surgery in the majority of patients. Only two patients (1 and 7) required an additional dose of rFVIIa, at 30 min and 75 min, respectively, with good results. Postoperative haemostasis was considered effective in 16 of 18 (89%) of the procedures performed in haemophilia patients, and ineffective in two patients because of excessive postoperative bleeding.

The pre-, peri- and postoperative periods were covered with rFVIIa alone in six haemophilia patients, while four patients received rFVIIa plus tranexamic acid. Other haemostatic measures (Cem-Ostetic™; Berkeley Advanced Biomaterials, Inc, Berkeley, CA, USA, gel foam and fibrin glue) were used in the patient who underwent excision of a jaw pseudotumour (Fig. 1). Fibrin glue was used to fill the area after percutaneous aspiration of a shoulder pseudotumour in one patient.

No thromboembolic events or disseminated intravascular coagulation were reported. Other complications were observed in four patients (Table 3). In one patient, a moderate bleed observed 15 min after the achillotenotomy was resolved by ligation of the damaged vessel, plus 5 days' rFVIIa treatment. The patient with Moore osteotomy presented with intermittent bleeding that was not controlled with higher doses of rFVIIa or pd-aPCC. No surgical cause of bleeding was found under anaesthesia during wound revision. As this patient's presurgical inhibitor titre was <5 BU, he was given recombinant factor VIII (rFVIII, Kogenate™; Bayer Healthcare Manufacturing, Berkeley, CA, USA), which stopped the bleeding. After 6 days, his anti-FVIII inhibitor titre rose and treatment was switched to rFVIIa every 4 h for 48 h. No re-bleeding occurred. After discharge, he continued prophylactic treatment with pd-aPCC (68 U kg^{-1} three times per week) and rFVIII (50 IU kg^{-1} three times per week) in order to start an immune tolerance induction regimen. A third patient presented with profuse, continuous bleeding 2 h after a hip and knee debridement. As his inhibitor titre was <5 BU after six doses of rFVIIa, FVIII was used for 6 days. No re-bleeding was observed, and the patient continued with rFVIII three times per week for immune tolerance induction. Treatment of the patient with VWD type 3 was considered effective, as no bleeding occurred during 6 days of rFVIIa treatment. After 48 h without treatment, a bleed was observed on the granulation tissue of the wound, which was treated with rFVIIa, monoclonal FVIII (HEMOFIL M™; Baxter Healthcare), fibrin glue, argon laser cauterization and tranexamic acid.

Discussion

Our report shows that both minor and major elective surgical procedures can be performed using rFVIIa as a first-line haemostatic treatment. Notably, there were no safety concerns and rFVIIa haemostasis was considered effective in 85% of the major procedures and 89% overall, in agreement with previously reported rates [8,18]. There were no thromboembolic events or disseminated intravascular coagulation in our patients, consistent with findings that such adverse events are

Table 2. Treatment characteristics of the surgeries.

Patient		Initial bolus dose of rFVIIa (μg kg^{-1})	Number of rFVIIa doses	Total rFVIIa dose (mg)	Treatment duration (days of haemostatic treatment)	Outcome
1	Surgical removal of haemophilic pseudotumour of the jaw	106	77	278.4	10	Effective
	Drainage of haemophilic pseudotumour of the fifth finger	106	77	184.8	10	Effective
2	Inguinal hernioplasty and surgical removal of epididymal cyst	111	68	316.8	8	Effective
3	Achillotenotomy	120	40	184.8	5	Effective
4	Percutaneous aspiration of pseudotumour in shoulder and resection of ear granuloma	115	40	216	5	Effective
5	Surgical reduction of a femur fracture	100	32	76.8	4	Effective
6	Debridement of necrotic wound in finger	90	32	57.6	4	Effective
	Amputation of first phalanx of finger	90	32	57.6	4	Effective
7	Moore osteotomy	120	60	266.8	12	Ineffective
8	Resection of anal fistula	120	60	600	6	Effective
9	Arthroscopic synovectomy of the knee	180	52	386	7	Effective
10	Achillotenotomy	115	42	304.8	5	Effective
11	Hip and knee debridement	126	6*	28.8	7†	Ineffective
12	Implantation of ureteral catheter	100	3	7.2	1	Effective
	Cytoscopy and removal of ureteral catheter	100	3	7.2	1	Effective
13	Chemical synoviorthesis (four procedures)	266	1	4.8	1	Effective

rFVIIa, recombinant activated factor VII.
*Number of doses until change to rescue treatment.
†Includes rFVIIa plus rFVIII treatment.

1. **Intraoper- ative haemostasis was achieved during surgery in the majority of patients. Only two pati...**
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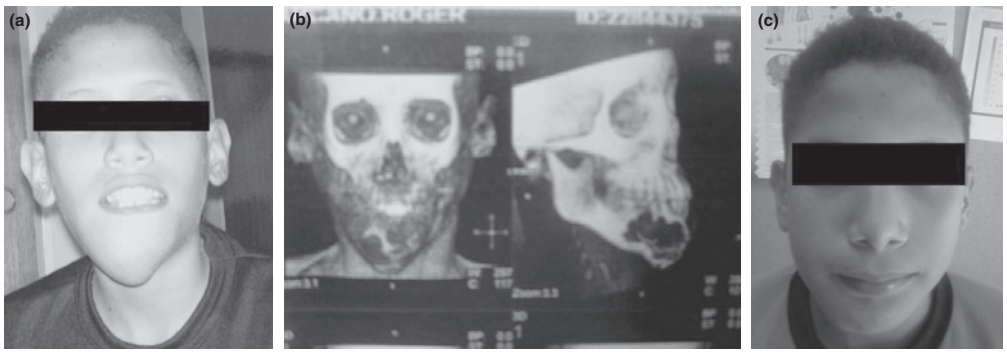

Fig. 1. Patient 1: Pseudotumour of the jaw. (a) Picture and (b) magnetic resonance imaging (MRI) presurgery and (c) patient 2 months after surgery.

Table 3. Details of patients with complications.

Patient	Elective surgery procedure	Complication	Number of rFVIIa doses until initiation of rescue treatment	Rescue treatment	RBC (U)
3	Achillotenotomy	Moderate bleed from broken vessel	3	Ligation of a ruptured vessel	None
7	Moore osteotomy	Profuse bleeding and wound haematoma 24 h after surgery, needing surgical revision	38	rFVIIa ~160 μg kg^{-1} × 3 pd-aPCC ~68 U kg^{-1} × 2 rFVIII 200 IU kg^{-1} initial dose rFVIII 140 IU kg^{-1} day^{-1} for 6 days	4
11	Hip and knee debridement	Profuse bleeding 2 h after surgery	6	rFVIII 200 IU kg^{-1} day^{-1}	3
8	Resection of anal fistula	Profuse bleeding 8 days after surgery	2 doses and continued ~100 μg kg^{-1} rFVIIa every 4–6 h for 6 days Total additional rFVIIa: 26 doses	Monoclonal FVIII 200–250 IU kg^{-1} day^{-1} Cauterization Fibrin glue	1

rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; rFVIII, recombinant factor VIII; RBC, red blood cell.

rare in haemophilia patients with inhibitors treated with rFVIIa [19].

Emergency or elective surgery in haemophilia patients with inhibitors were considered a significant challenge [20]. However, the emergence of rFVIIa has largely changed the management of inhibitor patients and many elective surgical procedures under rFVIIa haemostasis have now been reported [21,22]. Similar to the 89% efficacy in our cases, the overall efficacy with rFVIIa was excellent in 92% of major surgical cases reported by Ingerslev *et al.* [8] and in 81% and 86% of major and minor surgeries and 92% of dental procedures reported by Lusher *et al.* [18]. Furthermore, a review of published data suggested that rFVIIa is safe and effective when used to provide adequate haemostatic cover for inhibitor patients undergoing elective orthopaedic surgery [11]. Surgical haemostasis was achieved in the patient with VWD type 3, complicated with alloantibodies. Recombinant FVIIa has recently been recommended as a possible therapeutic approach for this rare group of patients [23].

In two of our patients, treatment was considered ineffective, which could be related to the rFVIIa dosing regimen, as this has yet to be optimized [11], or to other factors, such as concomitant medications with a potential antiplatelet effect. A recent consensus protocol recommends the use of higher doses of rFVIIa than used previously [24], with an initial bolus dose of rFVIIa of 120–180 μg kg^{-1} to cover surgery. Of the 13 major surgical procedures, there was good haemostatic control during surgery and an 'excellent' or 'extremely satisfactory' final outcome [24]. Another explanation for the lower rFVIIa efficacy in the two patients in our study could be related to inter-subject variability in responsiveness, which may be influenced by patient-specific factors and different mechanisms of action of different agents [6]. In our case series, the patients whose treatment was considered ineffective had a presurgical low inhibitor titre, and were thus treated successfully with high-dose FVIII until an anamnestic response occurred. It has been recommended that elective surgery should be deferred until the inhibitor titre has decreased

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spontaneously to <5 BU, to facilitate rescue therapy with FVIII [13,24,25]. Nevertheless, this strategy cannot be applied to all patients, and elective surgery – especially orthopaedic surgery – must be performed if it is indicated.

There is no consensus on the use of antifibrinolytics [26,27] or local haemostatic agents, but fibrin glue has been used successfully in our group to treat haemophilia cysts and pseudotumours [28,29].

In 2006, we started using rFVIIa in our centre to treat mild-to-moderate bleeding episodes, with successful results. Moreover, we had experience of using different therapeutic regimens for managing emergency surgeries in inhibitor patients, with variable outcomes. Our decision to perform elective surgery was based on the availability of rFVIIa and pd-aPCC in sufficient quantities to cover all eventualities. Use of pd-aPCC has been reported in case series [30,31], but has also been associated with an anamnestic response in up to 31.5% of cases [9]. Recombinant FVIIa does not contain FVIII, and therefore carries no risk of an anamnestic response [32].

Surgery in haemophilia patients can be emergency or elective. Complications, mainly haemorrhagic, may be observed even in patients with mild haemophilia. Thus, any surgical procedure is best performed in a specialized centre that has experience in the management of these patients [33], a specialized haemostasis laboratory and sufficient haemostatic agents to cover the entire treatment [14]. Haemostasis must be adequate throughout the entire procedure, and for several days thereafter to allow wound healing [14]. Involvement of a multidisciplinary team is required [34], both before and after the surgery, and good communication among team members (surgeons, anaesthesiologist and haematologist) is important. Elective surgery requires excellent presurgical evaluation and appropriate information, both for patients and their families [14].

Although the availability of bypassing agents has allowed more elective surgeries to be performed in haemophilia patients with inhibitors, some challenges remain, including optimization of dosing, use of bolus or continuous infusion and the lack of standardized monitoring methodologies. Currently no test can predict the clinical response to rFVIIa in individual patients, and the usefulness of global tests, such as thromboelastography or thrombin generation, is still under investigation in our group, and in other centres [35,36]. Therefore, the indication for surgery must be based on careful assessment of the benefit/risk ratio of the surgical procedure, as well as on orthopaedic considerations, such as chronic pain, immobility and the quality of life [37].

Conclusions

In our study, rFVIIa provided effective haemostatic cover, with no safety concerns, in elective surgery in haemophilia patients with inhibitors. Moreover, as the dosing regimen for rFVIIa is yet to be optimized, our findings provide much-needed evidence to add to this debate. Ultimately, given the complexity of treating haemophilia patients with high titre inhibitors, elective surgical procedures in this population should be performed under the supervision of a team experienced in managing this condition.

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Disclosures

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

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