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ORIGINAL ARTICLE

Elective orthopaedic surgery for haemophilia patients with inhibitors: single centre experience of 40 procedures and review of the literature

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Summary. With the introduction of safe and effective factor VIII/IX-bypassing agents – recombinant activated factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrates (pd-APCC) – elective orthopaedic surgery (EOS) is a viable option for haemophilia patients with inhibitors. We report a series of patients with haemophilia and inhibitors undergoing EOS between 1997 and 2008 using bypassing agents to provide haemostatic cover. All inhibitor patients undergoing EOS and receiving rFVIIa, plasma-derived prothrombin complex concentrates (pd-PCC) or pd-APCC as haemostatic cover were included. Patients were operated on by the same surgeon and were managed by the same haemophilia treatment centre. Forty procedures (25 minor and 15 major) were conducted in 18 patients. Twenty-one minor cases were covered using rFVIIa, three with pd-PCC, and one with pd-APCC; all major cases were covered using rFVIIa. Bleeding was no greater than expected compared with a non-haemophilic population in all 25 minor procedures. In the major procedure group, there was no excessive bleeding in 40% of cases (6/15) and bleeding completely stopped in response to rFVIIa. For the remaining nine cases, bleeding response to rFVIIa was described as 'markedly decreased' or 'decreased' in 4/15 cases and 'unchanged' in 5/15 cases. Overall, efficacy of rFVIIa, based on final patient outcome, was 85%. One death occurred as a result of sepsis secondary to necrotizing fasciitis. Good control of haemostasis can be achieved with bypassing agents in haemophilia patients with inhibitors undergoing minor EOS; rFVIIa was used as an effective bypassing agent, enabling EOS in patients undergoing minor and major procedures.

Keywords: elective orthopaedic surgery (EOS), haemophilia, inhibitors, plasma-derived activated prothrombin complex concentrates (pd-APCC), recombinant activated factor VII (rFVIIa)

Introduction

Patients with severe haemophilia frequently suffer from intra-articular haemorrhages, leading to pain, swelling, reduced motility and arthropathy, resulting in a significant reduction in quality of life [1]. When conservative measures have failed, the generally recommended approach is elective orthopaedic surgery (EOS) using clotting-factor replacement to prevent uncontrolled bleeding, reduce pain, restore mobility and function and minimize joint damage. However, approximately 20–25% of haemophilia A patients and 1–3% of haemophilia B patients have inhibitors to factor VIII or IX respectively; these patients represent a major therapeutic challenge to clinicians [2].

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Only 15 years ago, Robert Duthie, a distinguished orthopaedic surgeon, wrote that 'elective surgery is absolutely contraindicated in the presence of significant levels of FVIII antibodies' [3]. The general approach has been that surgery should be carried out only if absolutely necessary, i.e. in emergency situations. Indeed, for many people with haemophilia and inhibitors, concerns over intraoperative and postoperative bleeding complications discourage them from seeking EOS.

The bypassing agents, recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk A/S, Denmark), plasma-derived prothrombin complex concentrates (pd-PCC) and pd-activated prothrombin complex concentrates (pd-APCC) have been used for treatment of acute bleeding episodes in haemophilia patients with inhibitors [4,5]. The introduction of these agents has allowed elective interventions to be safely performed in a number of haemophilia patients with inhibitors, who would previously not have been recommended for elective orthopaedic surgeries [6].

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To date, three clinical trials using rFVIIa in haemophilia patients with inhibitors undergoing predominantly EOS have been reported [7–9], and these studies demonstrate the efficacy of the agent in this setting. However, the majority of data on the use of rFVIIa are derived from case studies. A number of case studies have reported on the successful use of rFVIIa as haemostatic cover during elective surgery in haemophilia patients with high-titer inhibitors [7,8,10–58]. In addition, results from a recent cost–benefit analysis suggest that major knee surgery using rFVIIa in haemophilia patients with inhibitors may be cost-effective because of the reduced number of bleedings or improved quality of life experienced by these individuals following surgery [59]. Pd-activated prothrombin complex concentrates and pd-PCCs have also been used to cover surgical procedures in haemophilia patients with inhibitors, although experience is largely based on minor EOS procedures [20–22,30,32,34,46,49,60–69]. While most case studies revealed positive outcomes with rFVIIa and pd-APCC, the small numbers of patients and potential selective reporting may bias results. In addition, it is rare that all cases are from a single institution, providing a homogeneous picture of patient responses with these agents.

We report here on one of the largest single-centre series of patients with haemophilia and inhibitors undergoing elective surgery using rFVIIa, pd-APCC or pd-PCC as haemostatic cover. In each case, surgery was performed by the same surgeon and the patient was under the care of the same haematologist, thereby reducing variability and allowing improved comparison with other studies.

Materials and methods

Patients

Patients included in this case series had severe haemophilia as defined by the World Federation of Haemophilia guidelines [2]. They were all inhibitor patients undergoing EOS and receiving either rFVIIa, pd-PCC or pd-APCC as haemostatic cover.

Study design

The surgical procedures were conducted by a single surgeon at a single centre – the Haemophilia Foundation, Buenos Aires, Argentina (the major haemophilia referral centre in Argentina, which receives patients from across the country) – between November 1997 and July 2008. All patients were under the care of the same haematologist. Each procedure was reported as a separate case. The study received Institutional Review Board/Ethics Committee approval.

Major and minor procedures were defined according to the Committee of Latin America on the Therapeutics of Inhibitor Groups (CLOTTING) guidelines [70]. Among orthopaedic procedures, only synoviorthesis, arthrocentesis, tenotomy and angiographic embolization are classified as minor; all other procedures were classified as major surgery.

Provision of haemostatic cover

The initial dose of rFVIIa, pd-PCC or pd-APCC was administered at the induction of anaesthesia, and continued at variable intervals throughout and after the procedure based on clinical criteria. In general, administration continued for 1–5 days after minor surgery and 7–14 days after major surgery [70]. The dose and schedule of rFVIIa administration was similar to that described by Giangrande *et al.* [71]. Patients received rFVIIa by bolus. Because of the larger clinical experience with rFVIIa, this agent was chosen for all patients undergoing major surgery [72].

Outcomes

To date, there has been no agreement on which efficacy parameters should be used to evaluate the haemostatic response to substitution therapy in surgical procedures or how best to determine outcomes immediately after such surgery.

In our analysis, a qualitative assessment of whether bleeding was greater than expected during surgery compared with a non-haemophilic population was made by the surgeon. The surgeon also provided a qualitative evaluation of bleeding after rFVIIa, pd-PCC or pd-APCC treatment ('stopped', 'markedly decreased', 'decreased', 'unchanged' or 'increased') as an overall assessment (as given in the 'Results', and also after each dose).

Given the heterogeneous population of major and minor procedures included in this series, the main outcome parameter used to assess the success of the surgical procedure was based on whether or not the patient was discharged following surgery (to their home, sometimes receiving ambulatory physiotherapy). If the patient was discharged, the procedure was considered effective. Other recorded outcomes were a requirement for additional surgery, or death following the procedure.

Patient follow-up after surgery occurred twice a month for 6 months, once every 3 months for the following 6 months, once every 6 months during the second and third years after surgery, and then once during the fourth year.

Data collection and analysis

A case-study template was used to collate data from each procedure to provide a comprehensive overview of

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the surgical procedure. The template requested information on patient age, gender, weight and blood pressure; bleeding history, type of surgery; all medications administered before and after the use of rFVIIa/pd-APCC/pd-PCC, including antifibrinolytic therapy and transfusion therapy (number of units of blood products, e.g. red blood cells, FFP, cryoprecipitate, platelets; volume of crystalloids/colloids); dose of rFVIIa/pd-APCC/pd-PCC, number of doses and interval between doses; assessment of bleeding after rFVIIa/pd-APCC/PCC treatment (classified as 'stopped', 'markedly decreased', 'decreased', 'unchanged' or 'increased'); adverse events or deaths, and whether these were related to bypassing agents (classified as 'probably or possibly related', 'unlikely related' or 'not related'). Whether or not an adverse event was considered related to bypassing-agent treatment was assessed by considering the event's temporal relationship with bypassing-agent agent administration together with other possible reasons for the event's occurrence.

Retrospective data were collected by one person and analysed independently. The case records were reviewed and case information was tabulated.

Results

Patient and procedure characteristics

A total of 40 orthopaedic procedures (25 minor and 15 major) were conducted in 18 male patients (Patients A–R). Table 1 summarizes the baseline patient and disease characteristics for each case and the surgical procedure conducted. The mean patient age was 17.3 years (range: 5–35 years). Most patients (16/18, 89%) had severe

Table 1. Details of the patients and procedures included in this study.

Patient: Procedure	Age (years)	Weight (kg)	Inhibitor titer (BU mL^{-1})	Haemostatic cover	Bolus dose (μg kg^{-1}*)	Subsequent doses (μg kg^{-1}) × no. doses
Minor procedures						
A1: Bilateral elbow radioactive synovectomy	9.0	25	74	rFVIIa	192	192 × 9
C1: Right knee ischiotibial deflexion tenotomy	8.9	24	37	rFVIIa	200	150 × 38
D1: Left knee radioactive synovectomy	16.0	60	7	rFVIIa	160	160 × 2
D2: Right elbow chemical synovectomy	10.2	32	7	PCC	2400 IU	2400 IU × 1
D3: Left elbow chemical synovectomy	10.2	32	7	PCC	1800 IU	1800 IU × 1
D4: Right elbow chemical synovectomy	10.9	32	7	PCC	2400	
D5: Right knee chemical synovectomy	15.1	50	7	rFVIIa	96	96 × 7
D6: Left knee chemical synovectomy	15.1	50	7	rFVIIa	96	96 × 3
D7: Left knee chemical synovectomy	15.2	50	7	rFVIIa	96	96 × 3
E1: Left shoulder chemical synovectomy	25.2	58	20	rFVIIa	103	103 × 5
E2: Left shoulder chemical synovectomy	25.2	58	20	rFVIIa	103	103 × 5
E3: Right shoulder chemical synovectomy	21.4	65		rFVIIa	74	74 × 7
E4: Right shoulder chemical synovectomy	21.6	60	16	rFVIIa	80	80 × 8
E5: Right knee chemical synovectomy	22.3	60	16	rFVIIa	100	100 × 1
E6: Right knee chemical synovectomy	22.4	57	16	rFVIIa	105	105 × 2
E7: Right knee chemical synovectomy	22.8	57	16	rFVIIa	126	126 × 2, 42 × 12
E8: Right shoulder chemical synovectomy	23.7	55	2	rFVIIa	109	109 × 2
F1: Knee radioactive synovectomy	5.3	16	59	rFVIIa	154	154 × 1
G1: Femoral angiography with subsequent embolization	12.7	33	4	APCC	121 IU kg^{-1}	6000 IU × 16
G3: Calcaneous angiography with subsequent embolization	12.7	33	160	rFVIIa	171	110 × 66
H1: Right ankle synovectomy	7.7	26	16	rFVIIa	270	270 × 1, 185 × 7
I1: Left knee embolization	16.4	61	23	rFVIIa	157	157 × 1, 116 × 21
J1: Right knee radioactive synovectomy	11.7	64	22	rFVIIa	150	150 × 8
J2: Right knee chemical synovectomy	12.7	77	2	rFVIIa	125	125 × 8
K1: Right knee radioactive synovectomy	15.9	56	35	rFVIIa	171	171 × 8
Major procedures						
B1: Right knee arthroscopic synovectomy	25.4	68	37	rFVIIa	200	200 × 3, 130 × 59
L1: Complicated pseudotumour with bone fractures	13.5	33	N/A	rFVIIa	140	106 × 32
M1: pseudotumour from right thigh	28.9	70	1127	rFVIIa	120	90 × 263
N1: Femoral osteotomy secondary to haemophilic arthroplasty	11.3	23	17	rFVIIa	200	156 × 16
O1: Surgical pseudotumour from right knee removal	13.1	25	94	rFVIIa	96	96 × 53
P1: Femoral osteotomy	16.0	60	99	rFVIIa	120	120 × 83
P2: Femoral osteotomy	16.0	60	99	rFVIIa	120	120 × 83
Q1: Arthroscopy to remove foreign body	27.3	65	28	rFVIIa	220	220 × 2, 148 × 57
Q2: Arthroscopy followed by arthrotomy	27.3	65	28	rFVIIa	220	220 × 2, 148 × 57
Q3: Right knee articular drainage	27.3	65	28	rFVIIa, APCC from Day 8	220	220 × 1, 185 × 2
G2: Right femoral surgical pseudotumour removal	12.7	33	4	rFVIIa	180	180 × 13
G4: Right calcaneous surgical pseudotumour removal	13.5	33	49	rFVIIa	150	150 × 1, 120 × 63
G5: Right calcaneous surgical pseudotumour removal	13.5	33	49	rFVIIa	150	150 × 1, 120 × 63
R1: Left femoral fracture osteosynthesis	35.6	70	4	rFVIIa	200	137 × 35
R2: Right femoral fracture osteosynthesis	35.6	70	4	rFVIIa	200	137 × 35

APCC, activated prothrombin complex concentrate; N/A, not available; rFVIIa, recombinant activated factor VII; PCC, prothrombin complex concentrate.
*Unless stated otherwise.

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Table 2. Bleeding response and patient outcome in inhibitor patients undergoing minor elective orthopaedic surgery.

Procedure (case identifier)	N	Bleed assessment*	Bleeding after treatment†	Patient outcome‡
Synovectomy§ (A1, D1–D7 E1–E8, F1, H1, J1, J2, K1)	21	Not > expected (all cases)	Stopped (all cases)	Discharged: rehab (all cases)
Tenotomy (C1)	1	Not > expected	Stopped	Discharged: home
Angiography with subsequent embolization¶ (G1, G3)	2	Not > expected (both cases)	Stopped (G3) Decreased (G1)	Additional surgery (both cases)
Embolization (I1)	1	Not > expected	Stopped	Discharged: rehab

N = number of procedures.
*Qualitative assessment of whether bleeding was greater than expected during surgery compared with a non-haemophilic population.
†Qualitative overall evaluation of bleeding after treatment with bypassing agent ('stopped', 'markedly decreased', 'decreased', 'unchanged' or 'increased').
‡Recorded outcomes included the patient being discharged [home (Discharged: home)/home with a requirement for ambulatory physiotherapy (Discharged: rehab)], a requirement for additional surgery, or death following the procedure.
§Cases D2–D4 were covered using plasma derived prothrombin complex concentrate.
¶Case G1 was covered using plasma-derived activated prothrombin complex concentrate.

haemophilia A with inhibitors; two patients (E and H) had severe haemophilia B with inhibitors.

Minor. A total of 25 minor procedures were performed in 10 patients: 21 synovectomies (11 knees, 4 elbows, 1 ankle and 5 shoulders), one knee tenotomy, one embolization and two cases (G1 and G3) of angiography with subsequent embolization (Table 1). Twenty-one cases were covered using rFVIIa, three cases were covered with pd-PCC (cases D2–D4) and one case was covered with pd-APCC (case G1).

For the cases covered using rFVIIa, the mean total dose was 60.7 mg (standard deviation [SD] = 59.7) and the mean number of doses was 12 (range 2–67 doses, SD = 15.2) per surgery. The mean individual dose was 5.9 mg (SD = 2.2) and the mean bolus dose was 169 μg kg^{-1} body weight. In the patient receiving pd-APCC (G1), a total dose of 52 000 IU was administered over a total of 17 doses. In the three cases in which pd-PCC was provided as cover (D2–D4), a total dose of 4800, 3600 and 2400 IU was administered over two, two and one dose(s) respectively.

Major. Fifteen major orthopaedic procedures were performed in nine patients: one arthroscopic synovectomy, six pseudotumour removals, two fixations of femoral bone fractures by osteosynthesis, three femoral osteotomies, one right knee articular drainage and two arthroscopies (Table 1). Recombinant FVIIa was used to provide haemostatic cover in all major surgical procedures. However, in one case (Q3), treatment was changed from rFVIIa to pd-APCC 8 days after surgery because of the payor's request.

The mean total dose of rFVIIa was 429.9 mg (SD = 477.8), the mean number of doses was 69 (range 14–264 doses, SD = 72.1) per surgery. The mean individual dose was 6.0 mg (SD = 2.7) and the mean bolus dose was 167.8 μg kg^{-1} body weight. In the patient who received rFVIIa followed by pd-APCC (Q3), a total rFVIIa dose of 620.2 mg was administered over a total of 63 doses during the first week. At Day 8, the patient was changed to pd-APCC, and subsequently received a total dose of 154 000 IU over 27 administrations.

Minor procedures

Efficacy. Efficacy outcomes according to the type of minor procedure are shown in Table 2. Bleeding was no greater than expected during surgery compared with a non-haemophilic population in all 25 minor procedures (100%). Bleeding was described as 'stopped' in response to the bypassing agent in 24 cases (96%). Bleeding was described as 'decreased' in one case (4%), G1, where cover was provided with pd-APCC.

In terms of patient outcome, a total of 23 cases (92%) were discharged following surgery. In the remaining two cases (G1 and G3) in a single patient, G, additional surgical interventions were required in which rFVIIa was used as coverage: one major procedure (G2) took place in the period between the minor cases, and two major procedures occurred after the minor cases (G4 and G5).

Safety. Adverse events were reported in two minor procedures (E1 and K1). Both events were mild re-bleeding and were considered unlikely to be related to rFVIIa.

Major procedures

Efficacy. Efficacy outcomes according to the type of major procedure are shown in Table 3. Bleeding was no greater than expected during surgery compared with a non-haemophilic population in 6/15 cases (40%, B1, L1, O1, G2, G4 and G5) (Fig. 1). In all six cases, bleeding completely stopped in response to rFVIIa (40%). For the remaining nine cases, bleeding response to rFVIIa was markedly decreased or decreased in 4/15 cases (27%, N1, R1, R2, Q3) and unchanged in 5/15 cases (33%, M1, P1, P2, Q1 and Q2). For case N1, the surgeon believed that the patient's poor nutritional status may have affected the response to rFVIIa.

In terms of patient outcomes, 11/15 cases (73%) were discharged. In most cases, patients were discharged following a standard hospitalization stay of 10–30 days

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Table 3. Bleeding response and patient outcome in inhibitor patients undergoing major elective orthopaedic surgery using recombinant activated factor VII as haemostatic cover.

Procedure (case identifier)	N	Bleed assessment*	Bleeding after treatment†	Patient outcome‡
Right knee arthroscopic synovectomy (B1)	1	Not > expected	Stopped	Discharged: home
Pseudotumour removal (L1, M1, O1, G2, G4, G5)	6	> expected (M1) Not > expected (L1, O1, G2, G4, G5)	Unchanged (M1) Stopped (L1, O1, G2, G4, G5)	Discharged: home (L1, O1) Discharged: rehab (G4, G5) Further hospitalization (G2) Death (M1)
Femoral osteotomy (N1, P1, P2)	3	> expected (all cases)	Decreased (N1) Unchanged (P1, P2)	Discharged: home (N1) Discharged: rehab (P1, P2)§
Fixation of bone fracture by osteosynthesis (R1, R2)	2	> expected (both cases)	Markedly decreased (both cases)	Discharged: rehab¶ (both cases)
Arthroscopy, with/without arthrotomy (Q1, Q2)	2	> expected (both cases)	Unchanged (both cases)	Scheduled for further surgery (articular drainage)
Articular drainage (Q3)	1	> expected	Decreased	Discharged: rehab

N = number of procedures.
*Qualitative assessment of whether bleeding was greater than expected during surgery compared with a non-haemophilic population.
†Qualitative overall evaluation of bleeding after treatment with bypassing agent ('stopped', 'markedly decreased', 'decreased', 'unchanged' or 'increased').
‡Recorded outcomes included the patient being discharged [home (Discharged: home)/home with a requirement for ambulatory physiotherapy (Discharged: rehab)], a requirement for additional surgery, or death following the procedure.
§Discharged with a requirement for physiotherapy 30 days postprocedure, but the patient died 6 months after surgery.
¶Discharged with a requirement for physiotherapy following admission to intensive care unit.

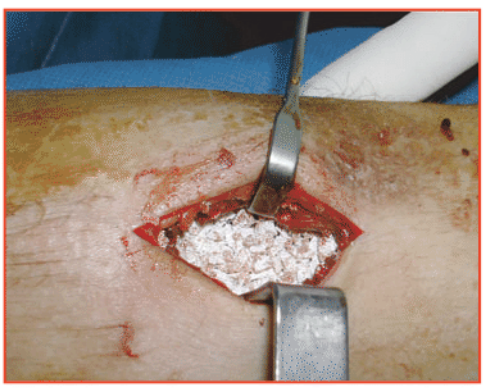

Fig. 1. Example of a clean surgical field following administration of recombinant activated factor VII during leg pseudotumour removal in a haemophilia patient with inhibitors.

for major procedures. However, patient R (simultaneous bilateral fixation of bone fractures by osteosynthesis, cases R1 and R2) suffered a gastrointestinal bleeding during hospitalization and went into shock; he was transferred to the intensive care unit and made a good recovery, following which he was discharged for rehabilitation. It is important to note that this patient experienced a severe gastrointestinal bleed with haemodynamic instability prior to surgery. Although haemostasis was initially achieved by FVIII, the clinical response deteriorated, and a subsequent blood test demonstrated increased levels of inhibitors (3.6 BU). Recombinant FVIIa was therefore used for haemostatic management during surgery.

In four cases (G2, M1, Q1 and Q2), patients were not discharged following the standard hospitalization stay postsurgery. For procedure G2 (surgical removal of a pseudotumour), the patient required an additional minor surgery (G3) and two further major procedures to treat a calcaneous pseudotumour (G4 and G5), the final outcome of which was referral for rehabilitation (G5). In case M1, the patient's overall condition was 'unstable' during and after the procedure, when the patient experienced persistent bleeding with hypovolemic shock. The pseudotumour in this patient was described as enormous; femoral destruction had occurred. The absence of soft tissue secondary to the extensive nature of the lesion was thought to have affected the haemostatic response to rFVIIa. The patient died as a result of sepsis secondary to necrotizing fasciitis. In patient Q, arthrofibrosis of the joint prevented the patient from completing rehabilitation following procedure Q1. Subsequent arthrotomy with debridement was conducted (Q2), during which bleeding was greater than expected and was not reduced by rFVIIa administration. Seven days after the procedure, the patient experienced severe pain with evidence of a tense haemarthrosis and bleeding from the wound drain. High doses of rFVIIa were required to decrease bleeding into the drain and to reduce pain at the operation site. In this case, the dose schedule was 170 μg kg^{-1} (5.64 mg) for one dose followed by doses of 110 μg kg^{-1} (3.6 mg) for 66 doses. The total rFVIIa dose administered was 245.04 mg. The patient underwent a third operation for articular drainage of the knee (Q3), following which he was referred for rehabilitation.

Safety. Adverse events were reported in five major procedure cases: four re-bleeding events (one mild, O1; one moderate, N1; two severe, P1 and Q2), and one superficial arterial thrombosis (G2). Mild re-bleeding was considered unlikely to be related to rFVIIa. For the three cases of moderate or severe re-bleeding, the physician considered the event possibly or probably

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related to rFVIIa. In case N1, the re-bleeding stopped and the patient was eventually discharged home; in case Q2, severe re-bleeding necessitated articular knee drainage (Q3, see efficacy results); in case P1, the bleeding stopped following clamping of the patient's drain without the need for additional intervention.

Patient G suffered a superficial arterial thrombosis in his posterior tibial artery, contralateral to the site of surgery, on Day 1–2 following procedure G2. Recombinant FVIIa was stopped and substitutive treatment with FVIII (100 IU kg^{-1} bolus and 100 IU kg^{-1} 24 h continuous infusion) was initiated. The event was not considered to be related to rFVIIa. The surgeon considered the event to be related to the patient's initial invasive minor procedure (G1 using pd-APCC as haemostatic cover), secondary to endothelial damage.

Two patients died in the major procedure group. One death occurred in a 28-year-old (M1), in whom rFVIIa was used as cover for the surgical removal of a giant pseudotumour from his right thigh. Death was caused by sepsis secondary to necrotizing fasciitis. The other death occurred 6 months after surgery in a 16-year-old patient (P) for reasons not related to the orthopaedic surgery. This patient fell from his wheelchair and sustained a small subdural haematoma 1 week after being discharged for rehabilitation. His wound re-opened and he developed a large haematoma on his right thigh. Recombinant FVIIa was re-administered at a dose of 120 μg kg^{-1} every 2 h. Although the subdural haematoma improved, bleeding continued from the wound, with subsequent infection and high transfusion requirements. The wound became more extensive, with evidence of tissue devitalization and muscle necrosis. Antibiotics were administered but muscle necrosis continued and the patient eventually died.

Use of other medications

As part of general practice at the Haemophilia Foundation, concomitant antifibrinolytic therapy is not used for orthopaedic surgery in inhibitor patients. Information on the use of blood products and antibiotics was available for 20 cases. Thirty per cent (6/20) of cases received blood products together with administration of rFVIIa or pd-APCC. Antibiotics were prescribed in 20% of cases (4/20).

Discussion

We report here the findings of our single-centre experience in patients with haemophilia with inhibitors undergoing elective surgery using either rFVIIa, pd-PCC or pd-APCC. Our data represent the largest series of major orthopaedic procedures conducted at a single centre. A total of 40 EOS were performed on 18 inhibitor patients – 25 minor procedures and 15 major procedures. Recombinant FVIIa was used for haemostatic cover in 36 cases (with change to pd-APCC at Day 8 postsurgery in one patient); pd-PCC was used in three cases, largely because of these procedures taking place prior to the approval of rFVIIa by the local regulatory authority; and pd-APCC was used in one case of minor surgery (angiography and embolization).

The number of doses of bypassing agents administered to the patients varied between the cases. Dosing schedules were agreed on a case-by-case basis prior to the surgery, with the intention of preventing major bleeding after the procedure. Consequently, it is not possible to retrospectively determine whether all the administered doses were required. The requirement for additional doses for breakthrough bleeds was not assessed. Cases C1, E7, G1, G3 and I1 received prophylactic dosing after the surgical procedure; this was based on previous history (in case E7, a right knee chemical synovectomy, it was decided to use prophylaxis because of the condition of the knee after two previous procedures in the same joint) or because at our centre, we use prophylaxis following embolization when arterial puncture is involved.

For patients who underwent minor procedures, in all cases bleeding observed during surgery was no greater than would be expected in a non-haemophilic population. For those cases treated with rFVIIa, all but one patient was discharged (92% of the procedures; 23/25). For the procedure treated with pd-APCC, further surgical intervention was required, with the patient undergoing an additional minor procedure and three major procedures, all of which used rFVIIa as haemostatic cover. In the major procedure group, bleeding was no greater than expected compared with a non-haemophilic population in 40% of the cases (6/15). In all six cases, bleeding completely stopped in response to rFVIIa. In the remaining nine cases, bleeding was greater than expected during surgery compared with a non-haemophilic population – bleeding was markedly decreased or decreased after rFVIIa in 27% (4/15) of the major procedures and unchanged in 33% (5/15) of the cases. In three of the cases in which bleeding was unchanged, the surgical outcome was still favourable, with the patients ultimately being discharged; in the other two instances, both of which involved the same patient, further surgery was scheduled – bleeding was decreased in the last of the surgical procedures and the patient was discharged afterwards. Indeed, in most major procedures (73%; 11/15), the patient was discharged. Overall, efficacy, considered in terms of patient outcome (discharge rates for the minor and major procedures), was 85% (34/40).

In the patients who underwent major surgery, one death occurred as a result of sepsis secondary to necrotizing fasciitis. However, this patient had an enormous pseudotumour, as well as femoral destruction. The patient's soft tissues proved inadequate to support reconstructive surgery or to facilitate wound

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healing. A second death was not related to the orthopaedic surgery.

It is appropriate to consider the limitations of our study. Currently, there are no widely agreed efficacy parameters that can be used to evaluate haemostatic response to bypassing agents during surgery – agreement on such parameters would enable comparisons to be made between studies. Moreover, the use of discharge status as the main outcome parameter used to assess the success of the surgical procedure might be considered to omit outcomes that would otherwise be considered as undesirable.

Our findings show that the use of bypassing agents, including rFVIIa, PCC and pd-APCC, as haemostatic cover can allow minor EOS procedures to be conducted safely and effectively in patients with high inhibitor titers. Moreover, rFVIIa allowed effective EOS procedures in patients undergoing major surgery. Recent recommendations highlight that in the absence of comparative studies of rFVIIa and pd-APCC in surgery, the choice of bypassing agent should be based on personal experience and agent availability [72]. Based on our experience, we recommend rFVIIa as a bypassing agent that allows effective EOS procedures in patients undergoing minor and major surgery.

In addition to the cases we have described in this study, numerous other case studies have been published, providing data on the use of rFVIIa and pd-APCC as haemostatic cover during elective orthopaedic procedures in haemophilia patients with inhibitors; most of these report on individual patients or small series of patients. We conducted a MEDLINE search in November 2008 (no time limits applied) to determine the number and type of EOS procedures in haemophilia patients with inhibitors described in the published literature. By cross-checking relevant articles, additional articles were added to the list in a non-standardized manner. Almost 60 articles were identified describing 332 EOS procedures [7,9–36,41,43–58,60–69,73–75]. Based on the classification of Perez Bianco *et al.* [70] in which synoviorthesis and arthrocentesis are classified as minor and all other procedures are classified as major, 210 (63%) of the procedures were major and 122 (37%) were minor EOS procedures. For the major procedures, 172 were covered with rFVIIa, 34 with pd-APCC and four with both agents. For the minor procedures, 87 were covered with pd-APCC, 34 with rFVIIa, and one where both agents were used. A further important study was excluded from this list because it included non-haemophilic patients with acquired inhibitors and minor procedures were confined to placement/removal of central venous catheters [8]. Based on these data, it is apparent that EOS has been performed routinely in haemophilia patients with inhibitors using bypassing agents as haemostatic cover. Recombinant FVIIa was used in the majority of EOS procedures, particularly in major surgeries (62% overall, 82% major procedures), whereas pd-APCC was primarily used in minor procedures (71%).

One of the most extensive single-centre case series previously reported is a series of 27 procedures in 26 patients reported by Rodriguez-Merchan *et al.* [21]. This described 20 radiosynoviortheses carried out using pd-APCC, and seven major orthopaedic procedures, four of which were performed with rFVIIa and three with pd-APCC. Based on the results obtained, the authors concluded that haemophilia patients with high inhibitor titers could undergo orthopaedic surgery with a high expectation of success. These results are in agreement with other reports by the same authors of EOS in 51 haemophilia patients with inhibitors from nine centres worldwide, also carried out using rFVIIa or pd-APCC as haemostatic cover [22,76].

Clinical trials examining rFVIIa dosing and continuous versus bolus administration are limited in haemophilia patients with inhibitors undergoing surgical procedures. In a prospective randomized trial, Shapiro *et al.* examined two doses (35 and 90 $\mu g\ kg^{-1}$) and concluded that the higher dose was an effective first-line option [8]. The pharmacokinetics of continuous infusion was investigated by Ludlam *et al.* in nine patients undergoing major EOS [7]. The authors reported that rFVIIa infusion at 50 $\mu g\ kg^{-1}$ per hour achieved continuous plasma FVII procoagulant activity in excess of 30 IU mL^{-1} (12–15 nmol L^{-1}) and provided adequate haemostatic control. In an open-label, randomized trial Pruthi *et al.* found that bolus injections of rFVIIa were similarly effective to continuous infusion among haemophilia patients with inhibitors undergoing a range of major operations [9].

How successful is use of rFVIIa in haemophilia patients with inhibitors undergoing EOS? A recent literature review examined data published between January 2002 and November 2006, identifying 12 articles including a total of 80 orthopaedic procedures [37]. In most cases, rFVIIa provided safe and effective haemostatic cover during orthopaedic surgery, with no bleeding complications. There was variation in the administered dose, although the majority of patients were treated with 90 $\mu g\ kg^{-1}$ bolus followed by either continuous infusion or bolus infusion. Of those cases reporting bleeding complications, most were considered to be related to an inadequate amount of rFVIIa; this highlights the need for greater understanding of dosages and procedures [29,42]. In 2004, the results of a consensus meeting on perspectives on surgery in haemophilia patients with inhibitors were reported, with recommended doses of rFVIIa (both in bolus injections and in continuous infusion) and pd-APCC for surgery being agreed [77]. A consensus protocol for the use of rFVIIa in EOS in haemophilia subjects has subsequently been published [71]. The protocol is based on a review of published data, as well as personal experience from a group of expert physicians. One of the key recommen-

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dations is an initial bolus dose of rFVIIa in the range of 120–180 μg kg^{-1} to cover surgery.

Conclusion

In the absence of clinical trials, data on the use of bypassing agents in haemophilia patients undergoing EOS is dependent on a thorough analysis of individual cases as part of a multidisciplinary team approach. Our case series shows that good control of haemostasis can be achieved with bypassing agents in haemophilia patients with inhibitors undergoing minor EOS. Based on our experience, we recommend rFVIIa as a bypassing agent that allows effective EOS procedures in patients undergoing minor and major surgery.

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