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Prospective, Randomised Trial of Two Doses of rFVIIa (NovoSeven) in Haemophilia Patients with Inhibitors Undergoing Surgery

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Summary

Recombinant factor VIIa (rFVIIa; NovoSeven®; Novo Nordisk) has proven efficacy in the treatment of haemophilic patients with inhibitors. This prospective, double-blind study compared rFVIIa (35 vs. 90 μg/kg) in the initiation and maintenance of haemostasis during and after elective surgery. Patients with inhibitors (FVIII, n = 26; FIX, n = 3) received rFVIIa immediately prior to incision; intraoperatively as needed; every 2 h for the first 48 h; and every 2-6 h for the following 3 days. Haemostasis was evaluated during surgery, at 0, 8, 24 and 48 h and 3, 4 and 5 days after wound closure. After day 5, open-label rFVIIa (90 μg/kg) was available for maintenance. Intraoperative haemostasis was achieved in 28/29 patients. All high-dose patients and 12/15 low dose patients had satisfactory haemostasis during the first 48 h. Twenty-three patients (13/14 high dose) successfully completed the study. Although the 35 μg/kg dose is probably sub-optimal for post-operative management, at least in major procedures, rFVIIa 90 μg/kg is an effective first-line option in surgery for patients with inhibitors.

Introduction

Haemostatic challenges in patients with haemophilia A and B are treatable with highly purified plasma-derived and recombinant DNA-derived factor VIII (FVIII) and factor IX (FIX) concentrates. However, a well-recognised and potentially life-threatening complication of haemophilia is the development of neutralising antibodies directed against the missing factor. Up to 25% of patients develop an inhibitor to FVIII, and 3-5% to FIX. This makes management of bleeding episodes difficult and poses a particular therapeutic challenge for elective or emergency surgical procedures.

To date, therapeutic interventions in these situations have included overwhelming the inhibitors with large doses of FVIII, but this is only feasible when the inhibitor titre is relatively low (1, 2). Other approaches have included the use of activated and non-activated prothrombin complex concentrates and porcine FVIII (3-6), plasmapheresis with or without absorption of antibody and, if time and resources permit, induction of immune tolerance (1). All these interventions can have significant drawbacks, including high cost, unpredictability of response, transmission of blood-derived infections, thromboembolic complications, and, in the case of porcine FVIII, development of anti-porcine antibodies. A therapy which can effectively produce haemostasis while eliminating or greatly reducing many, if not all, of these complications is needed.

Recombinant factor VIIa (rFVIIa; NovoSeven®; Novo Nordisk) potentially meets many of these requirements. As a recombinant product, it is not derived from human or animal plasma, thus eliminating the risk of human blood-transmitted diseases. It acts by enhancing the natural coagulation pathway by activating formation of the prothrombinase complex, and has a local action only in areas where tissue factor and/or phospholipid is exposed (7, 8). This has the advantage of limiting the extent of its activity to areas of injury and thus minimising the risk of disseminated intravascular coagulation (DIC) (7). The product has a predictable, well-characterised pharmacokinetic profile (half-life of 2.9 h) (9).

Recombinant FVIIa has been used in a compassionate-use programme in more than 400 patients with haemophilia A and B with inhibitors or with acquired inhibitors, involving over 1900 surgical and non-surgical bleeding episodes (10-14). It has been shown to be effective and well tolerated in the majority of these patients (11) with no evidence of an anamnestic response or of antibody formation against FVII (15). The non-surgical bleeding episodes included internal haemorrhage (12) and joint and muscle bleeds (14). Major and minor surgical procedures have been successfully undertaken in inhibitor patients treated with rFVIIa (16-18).

This paper describes a study conducted in the United States between July 1995 and July 1996 to compare the safety and efficacy of two dose levels of rFVIIa in attaining and maintaining effective haemostasis during and after elective surgical procedures.

Methods

Design

This was a double-blind, randomised, multicentre study of up to 5 days comparing two doses (35 μg/kg or 90 μg/kg) of rFVIIa. The study permitted the option of an open-label extension during which all patients received the same dose (90 μg/kg). The first 5 days constituted the primary study period during which efficacy was rated for blinded dosing.

Surgical procedures were prospectively defined as major or minor. The minor procedures were all placement and/or removal of central venous catheters; major procedures were mainly orthopaedic. Patients were randomised 1:1 within surgical categories to receive either dose of rFVIIa.

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Table 1 Haemostasis ratings at the various evaluation times

Evaluation time	Haemostasis rating
During surgery	Blood loss compared with a non-haemophilic rated as:
	As expected
	Less than expected
	More than expected
At wound closure (0 hours), and at 8, 24 and 48 hours after wound closure	Effective: bleeding stopped or substantially decreased
	Partially effective: bleeding reduced but continuing
	Ineffective: bleeding the same or worsened
Days 3 to 5 after wound closure	Adequate or not adequate

Inclusion and Exclusion Criteria

Four centres participated in the study. Eligible patients were recruited by the participating centres and the study sponsor. To be eligible for entry into the study, patients with haemophilia A or B with inhibitors or non-haemophiliac patients who had acquired inhibitors had to require preplanned elective surgery. Patient's inhibitor titre had to be either greater than 5 Bethesda Units or a titre that could not be over-ridden with 250 IU/kg FVIII or FIX. All patients signed (or, if a minor, had their legal guardian sign) an informed consent form prior to any study-related procedures. Key exclusion criteria included: no treatment with any investigational drug (other than rFVIIa) within the preceding 30 days or with any haemostatic agent (including rFVIIa) for 48 h prior to the preoperative rFVIIa dose; presence of other haemostatic disease; clinically significant abnormal blood biochemistry tests or platelet count below 100,000/mm^3; presence of significant systemic trauma; evidence of hypersensitivity to any of the study drug components; pregnancy or any physical or psychosocial abnormality considered significant by the investigator. Use of any haemostatic agent other than rFVIIa was not permitted during the study.

Treatment

Recombinant FVIIa was administered as an intravenous bolus just prior to intubation or incision; intraoperatively every 2 h or as needed by investigator discretion; and then every 2 h from wound closure (time 0) for the next 48 h. During this time, a single repeat blinded dose was allowed between each 2-h interval if haemostasis was considered to be inadequate. If, after a repeat dose, haemostasis was still unsatisfactory, open-label escape doses of up to 180 μg/kg could be given every 2 h until haemostasis was achieved or alternative treatment was deemed necessary.

After the first 48 postoperative hours, dosing was continued every 2 to 6 h for an additional 3 days. Although dosing was blinded during this period, infusion interval was investigator-determined.

After day 5, open-label product (90 μg/kg) was available to maintain haemostasis on a schedule determined by the investigator based on the nature of the surgical procedure and the patient's potential for delayed bleeding. The treatment period ended upon discharge from hospital with satisfactory haemostasis, requirement for alternative therapy or discontinuation due to an adverse event.

Vital signs (e.g. blood pressure, pulse and respiratory rates, and body temperature) were assessed in each patient prior to and after the preoperative dose and at regular intervals after wound closure.

Endpoints

The primary efficacy endpoint was the investigator's assessment of haemostasis at the surgical site during the operation, at wound closure, at 8, 24 and 48 h, and 3, 4 and 5 days after wound closure. The haemostasis ratings used at these times are given in Table 1.

The definition of satisfactory haemostasis included haemostasis ratings of effective or partially effective and maintained, while inadequate haemostasis was defined as a haemostasis rating of ineffective or not maintained. Treatment success was defined as completion of the study with satisfactory haemostasis. Treatment failure was defined as leaving the study due to a requirement for an escape dose of up to 180 μg/kg or alternative haemostatic treatment.

Adverse Events

Adverse events were defined as any undesirable event emerging during the study or an exacerbation of a pre-existing condition requiring active management. They were graded as serious or non-serious and by severity and relationship (if any) to the study drug. Serious side effects were those considered life threatening, permanently disabling, or requiring or prolonging hospitalisation.

Laboratory Assessments

Blood samples were taken for analysis of prothrombin time (PT), FVII coagulation activity (FVII:C; total FVII activity), fibrinogen, D-dimer, antithrombin III and platelet count. Samples were taken 10 min after the first dose and at 8, 24 and 48 h after wound closure.

Data Analysis

An intent-to-treat analysis was performed, using the Mantel-Haenszel χ^2 test with the last value carried forward procedure. This test was chosen in order to compare dose effects, adjusting for surgery type.

Ethical Considerations

The study was conducted in accordance with Good Clinical Practice guidelines and the US Code of Federal Regulations. Each patient (or their guardian if under 18 years old) gave written informed consent after the protocol was approved by the relevant ethics committee at each site.

Results

Demography

Twenty-nine eligible patients entered the study. There were 11 major surgical procedures: five synovectomies; two hip arthroplasties; one knee joint manipulation (with release of adhesions); one cartilage repair (knee); one bone graft (femur); and one laparoscopic renal biopsy. The 18 minor procedures included placement of central venous catheters (Broviac or Hickman) in eight cases, placement of other venous access devices (Port-a-Cath, LifePort etc) in nine cases and removal of a Port-a-Cath in one case.

All 29 patients were males; 25 had haemophilia A, three had haemophilia B and one had an acquired inhibitor to FVIII.

The race, haemophilia type and surgery type of the 15 patients given the low dose (35 μg/kg) were comparable to those 14 given the high

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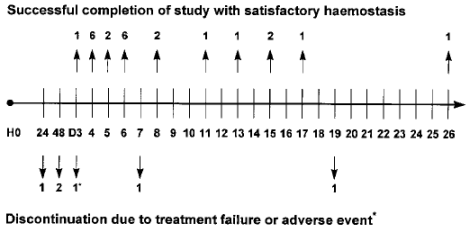
Table 2 Patient demography

Characteristic	No. (%) patients in each dose group		
	35 μg/kg (n = 15)	90 μg/kg (n = 14)	Combined (n = 29)
Age distribution (years)			
0-4	3 (20.0)	6 (42.9)	9 (31.0)
5-16	9 (60.0)	4 (28.6)	13 (44.8)
17-40	3 (20.0)	4 (28.6)	7 (24.1)
Race			
Caucasian	11 (73.3)	10 (71.4)	21 (72.4)
Black	4 (26.7)	4 (28.6)	8 (27.6)
Haemophilia A (with inhibitors)	13 (86.7)	12 (85.7)	25 (86.2)
Haemophilia B (with inhibitors)	1 (6.7)	2 (14.3)	3 (10.3)
Acquired antibody to FVIII	1 (6.7)	0 (0.0)	1 (3.4)
Minor surgery	10 (66.7)	8 (57.1)	18 (62.1)
Major surgery	5 (33.3)	6 (42.9)	11 (37.9)



* One patient discontinued on day 3 due to an adverse event

Fig. 1 Patient disposition. Figure shows successful outcomes and discontinuations on a timebase. H, hour; D, day

dose (90 μg/kg) (Table 2). One high-dose patient undergoing major surgery had received a haemostatic agent within 48 h of the preoperative rFVIIa dose. He was included in the analysis since the agent in question (Factor IX Alpha SD) had been administered approximately 36 h prior to the first rFVIIa dose.

Efficacy

Overall. Twenty-three of the patients successfully completed the study with satisfactory haemostasis (Fig. 1). Nine patients completed the study within the 5-day double-blind period.

Table 3 shows the number of patients with satisfactory haemostasis assessed during the double-blind period, in relation to dose given and surgery category. Patients who completed the study as successes prior to the end of the 5-day study period were contacted post-discharge to ascertain their clinical status regarding maintenance of haemostasis. All of these patients reported maintenance of haemostasis following discharge from hospital.

Five patients were regarded as haemostatic treatment failures, requiring escape dosing (up to 180 μg/kg) or alternative haemostatic therapy, and leaving the study without maintaining satisfactory haemostasis (Table 4). All but one of these patients were in the low-dose group.

Six patients required a blood transfusion: for decreased haemoglobin owing to bleeding during insertion of a central venous line (although this patient had more than expected blood loss, he went on to successfully complete the study); for volume expansion in a patient undergoing major orthopaedic surgery; for anaemia in a renal biopsy patient and an orthopaedic patient (subsequently withdrawn as a treatment failure); and for volume expansion and owing to blood loss in two orthopaedic patients (one of these patients was subsequently withdrawn due to treatment failure).

Intraoperative bleeding. Surgical blood loss was rated as less than expected or as expected in 28 patients. The only patient who bled more than expected had received 90 μg/kg for a minor procedure, but was considered to have satisfactory haemostasis at wound closure (Table 3).

Wound closure (hour 0). At wound closure, all major surgery patients were rated as having satisfactory haemostasis (Table 3). The only patient rated as having inadequate haemostasis had undergone a

Table 3 Number (%) of patients with satisfactory haemostasis (effective or partially effective) in each surgery and dose group (last value carried forward to account for patients who completed or discontinued the study)

	No. (%) patients in each dose group				
	Minor surgery		Major surgery		p-value
	35 μg/kg (n = 10)	90 μg/kg (n = 8)	35 μg/kg (n = 5)	90 μg/kg (n = 6)	35 μg/kg vs 90 μg/kg
Intraoperative	10 (100)	7 (88)	5 (100)	6 (100)	NS
Hour 0	9 (90)	8 (100)	5 (100)	6 (100)	NS
8	9 (90)	8 (100)	4 (80)	6 (100)	NS
24	10 (100)	8 (100)	4 (80)	6 (100)	NS
48	9 (90)	8 (100)	3 (60)	6 (100)	NS
Day 3	8 (80)	8 (100)	2 (40)	6 (100)	0.014
4	7 (70)	8 (100)	2 (40)	6 (100)	0.008
5	7 (70)	8 (100)	2 (40)	5 (83)	0.030

NS - not significant

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Table 4 Details of the six patients who left the study without achieving satisfactory haemostasis (treatment failures) or due to an adverse event*

Procedure	Dose group	Time of discontinuation	Alternative haemostatic therapy
Synovectomy and radial head excision	35 μg/kg	Hour 8-24	Porcine FVIII (28,525 units bolus with 12,240-14,640 units continuous infusion)
Capsulotomy and synovectomy	35 μg/kg	Hour 24-48	Recombinant FVIII (4000 units single dose followed by 4 units/kg/hour iv)
Port-a-Cath	35 μg/kg	Hour 24-48	Feiba (3100 units x 2; 6200 units q6h x 2 and q12h x 4)
Cartilage repair (knee arthroplasty)	90 μg/kg	Day 7	Feiba VH (unknown amount iv)
Hip replacement	35 μg/kg	Day 19	Aminocaproic acid (4-16 g q6h po)
Central venous catheter placement*	35 μg/kg	Day 3	None

* Patient discontinued due to an adverse event (thrombosis of internal jugular vein)

Table 5 Median duration of dosing, number of injections and total rFVIIa dose given by surgery category and dose group

	Minor surgery		Major surgery	
	35 μg/kg (n = 10)	90 μg/kg (n = 7)*	35 μg/kg (n = 5)	90 μg/kg (n = 6)
Median duration of dosing (days)	4.0	6.0	15.0	9.5
Range	3-6	3-6	2-26	8-17
Median number of injections	29.5	38.0	135.0	81.0
Range	24-44	26-67.0	11-186	71-128
Median total dose rFVIIa (mg)	45.5	67.0	656	569
Range	14-171	31-122	31-839	107-698

*Excluding one outlier who required 13 days' dosing and received a total rFVIIa dose of 706 mg in 98 injections. This patient had had a Hickman catheter insertion. If he is included, the median duration of dosing is unchanged (6.0 days) but the median number of injections rises to 39.5 and the median rFVIIa dose given rises to 80 mg.

minor procedure (Port-a-Cath placement) at a dose level of 35 μg/kg and subsequently required alternative therapy on day 2. However, at wound closure, this patient was not deemed to be a treatment failure.

Wound closure to hour 8. Haemostasis was satisfactory in 27 of 29 patients (Table 3). Inadequate haemostasis was recorded in one major surgical procedure (synovectomy of the left elbow and radial head excision) and one minor one (Port-a-Cath placement). In both cases the patients had been treated at the low dose level. However, they were maintained in the study; the major surgery patient received two additional doses of rFVIIa, and the minor surgery patient received one additional dose.

Hour 8 to hour 24 following wound closure. Inadequate haemostasis was again recorded in the low-dose patient undergoing synovectomy and radial head excision (Table 3). This patient was considered to have excessive bleeding after seven blinded doses and exited the study when he was given porcine FVIII (Table 4; Fig. 1).

Hour 24 to hour 48 following wound closure. Satisfactory haemostasis was recorded in 26 of the remaining 28 patients (Table 3). Bleeding was considered excessive in two patients, both of whom were given alternative therapy without having received an escape dose (Table 4; Fig. 1). One developed haemarthrosis after capsulotomy and synovectomy of the right knee. The second patient (Port-a-Cath placement) had required extra doses of rFVIIa during his procedure and during the first 8 h postoperatively. Both had been treated at the 35 μg/kg level.

Hour 48 to day 5 following wound closure. During this period, doses continued to be blinded but the dosing schedule was variable, at the discretion of the investigator. No patients exited during this time due to haemostatic problems. One patient successfully completed the study with satisfactory haemostasis on day 3, six patients on day 4 and two patients on day 5 (Fig. 1).

There was a statistically significant difference in efficacy from day 3 to day 5 in favour of the high-dose group compared with the low-dose group; p-values were calculated across both surgery categories and are shown in Table 3. Seventy percent of minor surgery patients in the low-dose group had satisfactory haemostasis by day 5, compared with 100% of high-dose, minor surgery patients. The difference between the dose groups was more pronounced in major surgery: 40% had satisfactory haemostasis with the low dose versus 83% with the high dose.

Treatment period after day 5. Six patients successfully completed the study on day 6, with a further eight completing between days 8 and 26. Two withdrawals due to bleeding occurred during the open-label phase when all patients received 90 μg/kg; one on day 7 and one on day 19 (Table 4; Fig. 1). The first of these patients had had a knee arthroplasty and had experienced satisfactory haemostasis with the high dose of rFVIIa until day 7 when he developed haemarthrosis in the operated joint. The second patient had also undergone major surgery, but had received the low dose. He had required transfusions both during and after the operation and was given escape doses on day 6. Despite having received escape doses, he was not withdrawn at this stage as a treatment failure. On day 12, he underwent debridement and reclosure of the wound, and placement of a central venous catheter. The wound was accidentally opened by the patient a week later and he was withdrawn on day 19.

Length of Treatment Period and Number of Injections

In the major surgery group, there was a clear reduction in the number of days of dosing required and the number of injections given to high-dose patients compared with those receiving the low dose (Table 5). However, the median total amount of rFVIIa given to major

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surgery patients was similar irrespective of dose group (Table 5). In minor surgery patients, the number of days' dosing, the number of injections and total rFVIIa dose given were similar in both dose groups (Table 5). There was one high-dose, minor surgery (Hickman placement) patient who required almost six times more rFVIIa than any other patient in this group. The investigator recorded that surgery had been difficult in this patient (this was the sole patient in whom bleeding during surgery had been greater than expected), and in fact the catheter was replaced on day 7.

Adverse Events

One patient had a clinically significant adverse event during the 5-day study period. This patient, who had received the 35 μg/kg dose, developed thrombosis of the right internal jugular vein on the second day following central venous catheter placement. The catheter was difficult to place, due to the patient having an anomalous venous system with a large internal jugular and an absent right external jugular vein, and this increased the amount of trauma experienced. Treatment with rFVIIa was discontinued on day 3 after he had received a total of 24 doses. There was no evidence of DIC in this patient.

Other recorded adverse events consisted of haemostatic treatment failures previously discussed. The only treatment-emergent effects on vital signs were ones attributable to anxiety, pain and/or the anaesthesia (e.g. decrease in intraoperative blood pressure and body temperature, and elevated pulse and respiratory rates).

Laboratory Assessments

FVII:C and PT. At 10 min following the preoperative dose, the mean increment in FVII:C for patients undergoing minor or major surgery was 13.64 U/ml (SD, 3.48) in those receiving the low dose and 30.5 U/ml (SD, 12.02) in the high-dose group, with comparable mean levels at subsequent testing times (Table 6). Mean PT fell from 12.67 s (SD, 1.18) to between 7.49 and 7.94 s during the postoperative period.

The times for blood sampling specified in the protocol meant that no FVII:C activity values were obtained at the time at which the investigator categorised a patient as a treatment failure, resulting in an inability to analyse FVII:C levels in terms of haemostatic outcome.

Parameters of DIC. D-dimer levels were elevated in the first 48 h postoperatively in 83% of patients (24 out of 29). The mean preoperative values were 0.7 μg/ml for the low-dose group and 0.8 μg/ml for the high-dose group. This compared with values of 1.1 and 1.7 μg/ml respectively after 48 h. No changes in mean level of antithrombin III were noted during the 48-h sampling period (mean preoperative value of 110.8% compared with 101.1% at 48 h). Mean fibrinogen levels increased slightly from preoperative levels of 311.7 mg/dl to 350.6 mg/dl at hour 48. No patient developed clinical or laboratory evidence of DIC. There was no change in mean platelet levels at the end of the study (314,1000/mm³) compared with preoperative levels (292,1000/mm³).

Table 6 Mean FVII:C levels according to dose group and surgery type

	FVII:C level (U/ml)			
	Minor surgery		Major surgery	
	35 μg/kg	90 μg/kg	35 μg/kg	90 μg/kg
Preoperative	2.52*	0.97	0.86	1.01
10 min postoperative	13.34	14.24	26.37	36.28
Hour 8	9.84	13.62	19.63	23.87
24	9.72	10.73	24.39	38.02
48	9.77	14.28	20.64	38.76

* One patient had a value of 12.2 U/ml

Discussion

Elective surgery in patients with inhibitors to FVIII or FIX is rarely undertaken, as this group of patients is at particularly high risk of intra- and postoperative bleeding complications. They are rarely, if ever, candidates for elective surgery, with consequent effects on mobility and quality of life. Thus, there is a clear and urgent need for a safe and effective haemostatic agent for use in these patients.

In the context of the bleeding hazards expected to be encountered in patients with coagulation disorders with or without inhibitors, the results of this study are particularly impressive. Twenty-three out of 29 patients successfully completed the study with satisfactory haemostasis. Over the total 5-day period of double-blind assessment, the majority of patients achieved and maintained satisfactory haemostasis, with 97% success intraoperatively.

The question of optimal dosage and dosing schedule for major and minor surgical procedures was not completely resolved by this study. A dose of 90 μg/kg was highly effective for patients undergoing both major and minor surgical procedures, with between 83% and 100% of patients having satisfactory haemostasis throughout the double-blind period. Even the 35 μg/kg dose provided haemostasis in virtually all minor procedures (70-100%, intraoperatively until day 5), with an apparent drop in efficacy towards the end of the double-blind period in major procedures (40% at day 5 compared with 80% at day 1). Overall, there was a statistically significant difference between the dosage groups in favour of 90 μg/kg in terms of the number of patients with satisfactory haemostasis from day 3 through day 5. Together with the lower number of injections and days of dosing required with the high dose in major surgery, this suggests that 90 μg/kg is a more effective dose to use, particularly for major surgical procedures.

Whether continuous infusion of rFVIIa would be more effective and drug-sparing remains an issue which needs to be addressed (19). However, until more effective laboratory measures of haemostatic effect are developed, we will have to rely on clinical assessment and its attendant variables as endpoints. As with this study, large numbers of relatively rare patients would need to be recruited and managed in strict accordance with a well-designed protocol.

In spite of the small number of patients and some study design problems, this study confirms the excellent efficacy of rFVIIa in these high-risk patients. In retrospect, the variable dosage schedules allowed after postoperative day 3 may have led to some difficulties in interpreting data, particularly regarding differences between doses and establishing optimal schedules.

Equally impressive as the efficacy in this study was the low rate of clinically or laboratory-defined adverse events. The patient who developed internal jugular thrombosis was also noted to have an anatomic abnormality, with subsequent difficulty in catheter placement and re-

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sultant increased vessel trauma; this could have contributed towards the thrombotic complication that developed. The absence of clinical evidence or laboratory changes indicating DIC is consistent with the mechanism of action of rFVIIa, which gives a local haemostatic effect. Levels of certain indicators of coagulation and fibrinolysis observed were comparable to those found in normal patients undergoing similar procedures (20-22). This is not surprising, considering that surgical procedures result in tissue damage, exposure of tissue factor, release of thromboplastic materials, and deposition of fibrin followed by physiological fibrinolysis.

The use of rFVIIa potentially overcomes the significant drawbacks associated with conventional replacement therapy for the treatment of patients with inhibitors. It is a new concept of therapy based on the idea of compensating for an impaired FVIII/FIX-dependent coagulation pathway by driving the FVII/tissue factor-dependent pathway which is the normal initiator of haemostasis. The addition of exogenous rFVIIa is thus a pharmacological treatment instead of conventional substitution therapy. Other benefits include no risk of viral transmission, lack of anamnestic response and a more local haemostatic effect.

This study is the most extensive to date of rFVIIa being used as first-line therapy in elective surgical procedures. Both the efficacy and drug related adverse event profiles in this study were similar to those reported when rFVIIa was assessed in the compassionate use programme in patients with inhibitors suffering from various bleeding episodes or undergoing surgery (16, 17, 23-25).

Based on the results of this study, rFVIIa appears to be an efficacious first-line agent in surgery. Excellent intraoperative haemostasis is achieved with either 35 μg/kg or 90 μg/kg. Although the 35 μg/kg is probably sub-optimal for postoperative management, at least in major procedures, 90 μg/kg is more effective for both minor and major procedures. More studies are needed to further define and refine an optimal dose schedule for surgical and non-surgical patients with inhibitors. In conclusion, the availability of this product with its powerful and local haemostatic action is an important advance in the treatment available for the management of these challenging patients.

References

1. Macik BG. Treatment of factor VIII inhibitors: products and strategies. Semen Thromb Hemost 1993; 19: 13-24.
2. Nilsson IM, Berntop E, Freiburghaus C. Treatment of patients with Factor VIII and IX inhibitors. Thromb Haemost 1993; 70: 56-9.
3. Bray G, Gomperts ED, Courter S, Gruppo R, Gordon EM, Manco-Johnson M, Shapiro A, Scheibel E, White G III, Lee M. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy and inhibitor risk in previously untreated patients with haemophilia A. The Recombinate Study Group. Blood 1994; 83: 2428-35.
4. Brettler DB, Forsberg MS, Levine PH, Aledort LM, Hiltgartner MW, Kasper CK, Lusher JM, McMillan C, Roberts H, on behalf of the Cooperating Investigators. The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. Arch Intern Med 1989; 149: 1381-5.
5. Hay CRM, Lozier JN, Lee CA, Tradati H, Santagostino E, Ciavarella N, Schiavoni M, Fukiu H, Yoskioka A. Porcine factor VIII in patients with congenital hemophilia and inhibitors: efficacy, patient selection and side effects. Semin Hematol 1994; 31: 20-5.
6. Lusher JM. Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors – benefits and limitations. Semin Hematol 1994; 31: 49-52.
7. Rao LVM, Rapaport SI. Activation of factor VII bound to tissue factor: a key early step in the tissue factor pathway of coagulation. Proc Natl Acad Sci USA 1988; 85: 6687-91.
8. Brinkhous KM, Hedner U, Garris JB, Diness V, Read MS. Effect of recombinant factor VIIa on the hemostatic defect in dogs with hemophilia A, hemophilia B, and von Willebrand disease. Proc Natl Acad Sci USA 1989; 86: 1382-6.
9. Lindley CM, Sawyer WT, Macik BG, Lusher J, Harrison JF, Baird-Cox K, Birch K, Glazer S, Roberts HR. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. Clin Pharmacol Ther 1994; 55: 638-48.
10. Hedner U, Glazer S. Management of hemophilia patients with inhibitors. Hematol Oncol Clin North Am 1992; 6: 1035-46.
11. Roberts H. Clinical experience with recombinant factor VIIa (Novo Seven®): summary of efficacy and safety. Haemophilia 1996; 2: 63.
12. Lusher JM. Recombinant factor VIIa (NovoSeven®) in the treatment of internal bleeding in patients with factor VIII and IX inhibitors. Haemostasis 1996; 26: 124-30.
13. Rice KM, Savidge GF, NovoSeven® (Recombinant factor VIIa) in central nervous system bleeds. Haemost 1996; 26: 131-4.
14. Mølskov Bech R. Recombinant factor VIIa in joint and muscle bleeding episodes. Haemostasis 1996; 26: 135-8.
15. Nicolaisen EM, Hansen LL, Poulsen F, Glazer S, Hedner U. Immunological aspects of recombinant factor VIIa (rFVIIa) in clinical use. Thromb Haemost 1996; 76: 200-4.
16. Hedner U, Glazer S, Pingel K, Alberts KA, Blomback M, Schulman S, Johnsson H. Successful use of recombinant factor VIIa in patients with severe haemophilia A during synovectomy. Lancet 1988; ii: 1193.
17. Ingerslev J, Freidman D, Gastineau D, Gilchrist G, Johnsson H, Lucas G, McPherson JJ, Preston E, Scheibel E, Shuman M. Major surgery in haemophiliac patients with inhibitors using recombinant factor VIIa. Haemostasis 1996; 26: 118-23.
18. O'Marcaigh AS, Schmalz BJ, Shaughnessy WJ, Gilchrist GS. Successful hemostasis during a major orthopedic operation by using recombinant activated factor VII in a patient with severe hemophilia A and a potent inhibitor. Mayo Clin Proc 1994; 69: 641-4.
19. Schulman S, Bech Jensen M, Varon D, Keller N, Gitel S, Horoszowski H, Heim M, Martinowitz U. Feasibility of using recombinant factor VIIa in continuous infusion. Thromb Haemost 1996; 75: 432-6.
20. Egan EL, Bowie EJW, Kazmier FJ, Gilchrist GS, Woods JW, Owen CA Jr. Effect of surgical operations on certain tests used to diagnose intravascular coagulation and fibrinolysis. Mayo Clin Proc 1974; 49: 658-64.
21. Gaffney PJ, Creighton LJ, Callus M, Thorpe R. Monoclonal antibodies to crosslinked fibrin degradation products (XL-FDP). II. Evaluation in a variety of clinical conditions. Br J Haematol 1988; 68: 91-6.
22. Van Wersch JW, de Vries-Hanje JC, Oosterbos C. Coagulation activation and reactive fibrinolysis in patients receiving oral anticoagulation after total hip or knee replacement. Blood Coag Fibrinol 1994; 5: 604-8.
23. Schmidt ML, Gamerman S, Smith HE, Scott JP, DiMichele DM. Recombinant activated factor VII (rFVIIa) therapy for intracranial hemorrhage in hemophilia A patients with inhibitors. Am J Hematol 1994; 47: 36-40.
24. Glazer S, Hedner U, Falch JF. Clinical update on the use of recombinant factor VIIa. Proceedings of the 2nd International Symposium on inhibitors to coagulation factors. Aledort LM, White GC, eds. New York: Plenum Publishing Corp 1993; 163-74.
25. Bell BA, Birch K, Glazer S. Experience with recombinant factor VIIa in an infant hemophilia with inhibitors to FVII:C undergoing emergency central line placement. Am J Pediatr Hematol Oncol 1993; 15: 77-9.

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