

Use of recombinant factor VIIa for emergency reversal of anticoagulation

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ABSTRACT

Context: There is limited data regarding the use of activated recombinant factor VII (rFVIIa) in anticoagulated patients requiring reversal. **Aims:** To identify and describe characteristics of subjects who received rFVIIa as part of emergency treatment aimed at improving hemostasis. **Settings and Design:** Data was obtained from an international peer-reviewed registry haemostasis.com. This registry contains data reported by physicians, who had elected to use rFVIIa to control bleeding in an emergency clinical situation. The contributors' approval for inclusion in the study was obtained and they were requested to validate and update information. **Materials and Methods:** Database review of cases receiving rFVIIa to manage bleeding coherent with the use of anticoagulant therapy. **Statistical Analysis:** The Wilcoxon signed rank test was used to compare requirements for blood products and crystalloids/colloids during the 24h preceding and following rFVIIa administration, as well as changes in the levels of clotting factors during that period. **Results:** Eighteen patients were treated with rFVIIa (median dose: 87.35 $\mu\text{g}/\text{kg}$; range: 20.0-106.0 $\mu\text{g}/\text{kg}$) for bleeding. Anticoagulants requiring reversal included low-molecular-weight heparin (n = 6), unfractionated heparin (n = 8), coumarin (n = 3) and warfarin (n = 1). All patients had failed to respond to traditional antidotes and blood products. Following administration, bleeding stopped in 10, markedly decreased in five and slowed in the remaining three. Amongst 12/16 patients, a response was observed within 2.0 h of first administration. The requirement for blood products and crystalloids/colloids decreased ($P < 0.05$) after rFVIIa administration. rFVIIa was well tolerated. **Conclusions:** rFVIIa may play a role in control of untoward bleeding in subjects receiving anticoagulation therapy.

KEY WORDS: Anticoagulation therapy, bleeding, recombinant activated factor VII, rFVIIa

Anticoagulation for prevention and treatment of thromboembolism is achieved with the help of agents such as warfarin, acenocoumarol (coumarin), unfractionated heparin (UFH) and low molecular weight heparins (LMH). Patients on anticoagulation therapy may require rapid reversal of anticoagulation in the event of life-threatening hemorrhage or when invasive procedures need to be undertaken. Currently available methods of reversal have serious limitations or are beset with several disadvantages. For example, Vitamin K reverses the effects of warfarin and coumarin, but takes several hours to achieve clinical effect. More rapid reversal of anticoagulation may be achieved by infusion of either fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs). However, these agents are inconsistent in their action on INR or PTT, require a long time for commencement of effect

and several patients are unable to tolerate the massive volumes that need to be transfused. In addition PCCs may be thrombogenic.^[1] Protamine can reverse the effects of UFH, but has limited ability in reversing the anticoagulant effects of LMWH and also carries a risk of allergic reactions.^[2,3] FVIIa (rFVIIa) (NovoSeven[®]; Novo Nordisk A/S, Bagsvaerd, Denmark) has the potential to act as a hemostatic agent in patients requiring anticoagulant reversal. Although there are reports citing its use in the management of acute hemorrhage in situations such as platelet disorders,^[4-6] congenital FVII deficiency,^[7] cardiac surgery,^[8] trauma,^[9] intracerebral bleeding,^[10] liver transplantation^[11] and obstetric practice,^[12] there is only a case report describing the use of rFVIIa for heparin reversal.^[16] As ethical and practical difficulties preclude a systematic study of a new drug in patients suffering from clinically significant anticoagulant-related hemorrhage, this study was undertaken to collate the experiences of a number of physicians using rFVIIa.

See editorial on page no. 3, 4

Materials and Methods

Haemostasis.com is an international, internet-based registry established to gather voluntarily submitted data on the investigational use of rFVIIa.^[17] It is independently managed and supervised by a steering committee of medical experts. Individual physicians entered information regarding off-label use of rFVIIa onto the *haemostasis.com* website between June 2001 and December 2003 using a password. An automated search of the registry was undertaken to identify all cases of anticoagulation-related bleeding treated with rFVIIa using the search term ‘coagulopathy, anticoagulant reversal, other’. These records were manually cross-checked against monthly summary reports of new entries, produced by the registry administrator.

Case providers were requested to complete a registry template on the *haemostasis.com* website and provide the following information: patient age, sex, actual body weight and underlying condition; bleeding severity (subjectively classed as mild, moderate or severe); all medications administered, including platelet transfusions before and after rFVIIa administration; dosage of rFVIIa, number of doses and interval between doses; bleeding response to rFVIIa (subjectively classed as stopped, markedly decreased, slowed, no change, increased) and time to response; adverse events and whether these were related to rFVIIa; results of laboratory tests (Hb, INR, PT, APTT, fibrinogen); patient outcome; and a brief case description. Permission to include a case was obtained from the respective treating physician. Patients with inadequate data were excluded from analysis. The authors reviewed the patient records, then tabulated and analyzed the case information.

As no formal clinical investigation was undertaken and *haemostasis.com* serves only as a repository, ethical committee approval was not sought. The primary outcome under examination was cessation of hemorrhage. Secondary outcomes were changes in fluid requirement and hematological parameters. The Wilcoxon signed rank test was used to compare administration of blood products and crystalloids/colloids during the 24h before and after injection of rFVIIa, as well as changes in clotting factors.

Details of 18 patients entered into *haemostasis.com* who experienced anticoagulant-related bleeding treated with rFVIIa are presented here.

Results

A search of *haemostasis.com* identified 27 patients satisfying the inclusion criteria. All of them received rFVIIa as a rescue therapy for bleeding during or after a surgical or invasive procedure. Nine patients were excluded because it was not possible to validate results and/or obtain permission for their inclusion from the case providers. However, the demographic characteristics of cases not included were quite similar to the group of patients included. The patient and treatment characteristics of the 18 patients analyzed are summarized in Table 1. These patients received a median dose of rFVIIa of

87.35 µg/kg (range: 20.0-106.0 µg/kg. All but one patient received a single dose of rFVIIa.

Efficacy

Treatment with rFVIIa was associated with cessation of bleeding in ten cases. Bleeding was markedly decreased in another five, while it slowed considerably in three patients. In 12/16 patients, improved hemostasis occurred within two hours of receiving a single dose of rFVIIa (interval not recorded in one patient). In patient 15, response was observed within two hours of the second dose. Neither the initial severity of the bleed, nor the dose of rFVIIa administered appeared to determine the efficacy of treatment.

Administration of other agents

Half the patients included in this series received anticoagulation antidotes other than rFVIIa. There was no indication that the administration of these agents influenced the overall bleeding outcome. Seventeen patients were infused replacement blood products (packed cells, whole blood, FFP, cryoprecipitate or platelets) and 12 patients received crystalloids or colloids in the 24h before rFVIIa administration. The use of replacement blood products ($P < 0.001$) and fluid therapy ($P < 0.05$) were significantly reduced in the 24h after administration of rFVIIa [Figure 1].

Hematological parameters

Improvements in hematological parameters were generally seen following administration of rFVIIa [Figures 2 and 3]. Where data was available, decreases in INR [$P < 0.01$; Figure 1] and PT values [$P < 0.05$; Figure 3] were observed.

Patients 1 and 3 underwent cardiac surgery during establishment of extracorporeal circulation (ECC); UFH was administered peri-operatively to prevent ECC-related clotting. In these subjects pre and postsurgery APTTs values increased from 34s to 76s and from 38s to 57s respectively after receiving rFVIIa.

Three of six patients receiving LMWH had evidence of

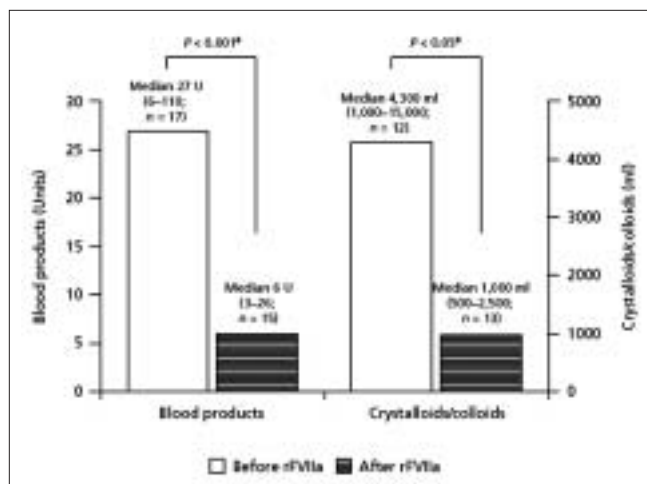


Figure 1: Median quantities of blood products and crystalloids/colloids given to patients in the 24h before and after receiving rFVIIa. Wilcoxon signed rank test

Table 1: Summary of patient characteristics, treatments and response to rFVIIa

Patient	Age sex	Co-morbidity	Reason for anticoagulation	Reason for rFVIIa administration	Degree of bleeding	Type of anti-coagulant	Dose rFVIIa µg/Kg body weight	Other administered agents	Effect on bleeding (time to effect after rFVIIa)
1	77M	Renal artery stenosis, AAA, COPD, hyper-lipidemia, coagulopathy	Mitral valve insufficiency, angina	Aortocoronary bypass, mitral valve replacement: peri- and post-operative bleeding	Severe	UHF	80.0	Protamine, fibrin sealant, tranexamic acid, aprotinin	Stopped (1h)
2	54M	Coagulopathy	Aortic stenosis	Valve surgery: postoperative bleeding	Severe	UHF	36.0	Protamine, tranexamic acid	Stopped (6h)
3	60M	Hypertension	Ischemic heart disease, unstable angina	Aortocoronary bypass for myocardial infarction: peri- and post-operative bleeding	Severe	UHF	57.9	Protamine, tranexamic acid, aprotinin	Stopped (2h)
4	72M	Pneumonia, hypertension, liver disease, coagulopathy, thrombocytopenia, collagen disease, pancreatitis, DIC	Stroke	Central venous catheter insertion and fasciotomy: hematoma in neck and uncontrollable bleeding from arm	Severe	LMWH	89.0	Tranexamic acid	Stopped (0.5h)
5	69M	Extended ECC, anemia	Valvular disease, ischemic heart disease	Valve surgery: postoperative bleeding	Moderate	UFH	31.2	Tranexamic acid	Slowed (7.5h)
6	45M	Duodenal ulcer, thrombocytopenia	Valvular disease, ischemic heart disease	Acute upper GI bleeding from duodenal ulcer following anticoagulant overdose	Severe	Warfarin	85.7		Stopped (1h)
7	56M	Hypertension, DIC	Valvular disease, ischemic heart disease	Valve surgery for chronic infectious endocarditis: pre- and peri-operative bleeding	Severe	LMWH	83.4	APCC, aprotinin	Stopped (NR)
8	72M	Peripheral vascular disease, thrombocytopenia, coagulopathy	Valvular disease, ischemic heart disease, aortic stenosis, dilatation of ascending aorta	Valve surgery, replacement of ascending aorta, CABG: postoperative bleeding	Severe	Coumarin	81.0	PCC, AT, fibrin sealant, aprotinin	Markedly decreased (7.8h)
9	55M	Fatty liver	Extensive thrombotic history	Administration for GI bleeding before TIPPS procedure for gastric varices and mesenteric venous thromboses	Severe	Coumarin	90.0		Slowed (2h)
10 ^a	18F	Burkitt's lymphoma, chemotherapy-induced thrombocytopenia	DVT	Extraction of lymph nodes, resulting in inguinal necrosis and bleeding: post-operative bleeding	Severe	LMWH	20.0		Stopped (1h)
11	76M	Hypertension, platelet dysfunction	Myocardial infarction, unstable angina	CABG for triple vessel disease: bleeding from mediastinal drain	Moderate	UFH	94.4	Protamine, aminocaproic acid, aprotinin	Markedly decreased (1.25h)
12	72M	Hypertension	Ischemic heart disease	CABG: post-operative oozing from drains	Moderate	UFH	91.4	Aprotinin	Markedly decreased (2h)
13	60M	Hyperlipidemia, hypertension, platelet dysfunction, DIC, on aspirin	Ischemic heart disease	CABG and Bentall's procedure for triple vessel disease and aortic regurgitation: bleeding from mediastinal drain	Moderate	UFH	99.0	Protamine, aminocaproic acid	Markedly decreased (1h)
14	76M	COPD, pleurisy, gastric ulcer, thrombocytopenia, coagulopathy	Valvular disease	Mitral valve surgery: diffuse postoperative bleeding	Severe	LMWH	91.0		Stopped (1h)
15	69M	Hypertension, thrombocytopenia	Aortic aneurysm	Emergency aortic replacement under DHCA: postoperative bleeding	NR	UFH	91.4	Tranexamic acid, aprotinin	Markedly decreased (1.8h after second dose rFVIIa)

Table 1: (Continued) Summary of patient characteristics, treatments and response to rFVIIa

Patient	Age sex	Co-morbidity	Reason for anticoagulation	Reason for rFVIIa administration	Degree of bleeding	Type of anti-coagulant	Dose rFVIIa $\mu\text{g}/\text{Kg}$ body weight	Other administered agents	Effect on bleeding (time to effect after rFVIIa)
16	16F		Cystic fibrosis	Lung transplantation with extracorporeal membrane oxygenation: postoperative bleeding	Severe	Heparin	106.0	Aprotinin	Stopped (1h)
17	61F	Hypertension, diabetes, goitre	Resection of spinal cord tumor	Postoperative hemorrhagic shock	Severe	LMWH	85.0	AT,	Slowed (0.3h)
18	26M	Post-MUD BMT for MDS, bleeding tendency, chronic renal failure on dialysis	Hip replacement	Postoperative bleeding following drain removal	Moderate	LMWH	98.0	APCC, tranexamic acid	Stopped (24h)

AAA: Abdominal aortic aneurysm; APCC: Activated prothrombin complex concentrate; AT: Antithrombin; BMT: Bone marrow transplant; CABG: Coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; DHCA: Deep hypothermic circulatory arrest; DIC: Disseminated intravascular coagulation; ECC: Extracorporeal circulation; DVT: Deep vein thrombosis; F: Female; GI: Gastrointestinal; LMWH: Low-molecular-weight heparin; M: Male; MDS: Myelodysplastic syndrome; MOF: Multiple organ failure; MUD: Matched unrelated donor; NR: Not recorded; PCC: Prothrombin complex concentrate; TIPSS: Trans-jugular intra-hepatic porto-systemic stent-shunt; UFH: Un-fractionated heparin, *Patient 10 is also described in Brenner *et al*^[30] and Eùliæ *et al*^[31]

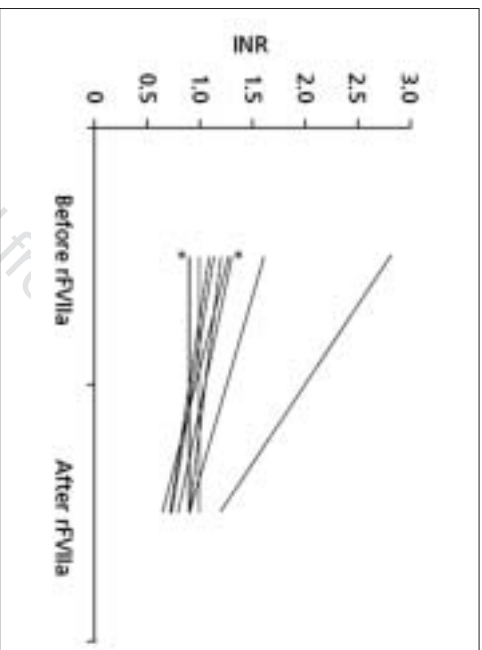


Figure 2: International normalized ratio (INR) before and after rFVIIa administration ($n = 11$); $P < 0.01$ (overall; Wilcoxon signed rank test). *Lines represent data on two patients each

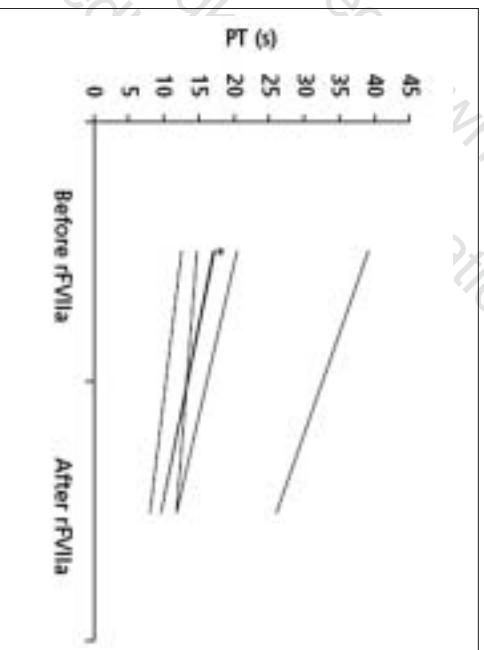


Figure 3: Prothrombin time (PT) before and after rFVIIa administration ($n = 6$); $P < 0.05$ (overall; Wilcoxon signed rank test). *Lines represent data on two patients

thrombocytopenia prior to the bleeding episode described here (patients 4, 10 and 14). In Patient 10, thrombocytopenia was attributed to chemotherapy for Burkitt's lymphoma.

Fibrinogen levels generally increased following IV rFVIIa (preadministration: median, 2.7 g/l; range, 0.5-5.1 g/l; $n = 12$; postadministration: median, 3.5 g/l; range, 1.6-6.0 g/l; $n = 10$). Similarly, hemoglobin levels rose in the majority of subjects (preadministration: median, 9.1 g/dl; range, 5.3-13.9 g/dl; $n = 17$; postadministration: median, 10.03 g/dl; range, 7.0-12.8 g/dl; $n = 17$).

Final outcome

Final outcome was recorded in 14 patients: eight patients were discharged from the hospital, one patient remained in intensive care and five patients died (multiple organ failure: two, cardiac failure, hemorrhagic shock and undetermined cause one each).

Adverse events

All deaths were considered to be 'unrelated to rFVIIa'

administration. rFVIIa was well tolerated and no adverse events were reported.

Discussion

rFVIIa is thought to act primarily by binding to the surface of activated platelets at the site of injury leading to the formation of a stable, localized clot. It was originally developed for the treatment of bleeding episodes in patients with hemophilia A or B. Limited data available indicates that rFVIIa could be of value in emergency anticoagulant reversal in a wide range of clinical situations. Various studies have shown that it is effective in normalizing PT and controlling warfarin-induced bleeding in animal models,^[13] normalizing INR and PT in healthy volunteers receiving acenocoumarol, decreasing INR in nontraumatic, warfarin-related acute intracranial hemorrhage^[14] and preventing bleeding when administered prophylactically to patients with deficiency of vitamin K-dependent factors.^[15]

This study suggests that administration of rFVIIa may be of value in anticoagulated subjects suffering significant hemorrhage unresponsive to conventional measures. Our findings need to be interpreted with care in view of a number of methodological limitations and difficulties in establishing a direct link between rFVIIa and hemostasis. Patients in this series are heterogeneous (receipt of different anticoagulants and other therapies, voluntary registration of subjects which may have led to a bias in enrolment and presence of incomplete or subjective data with regards to degree of bleeding). On the plus side, our hypothesis is supported by the fact that prior hemostatic treatments were unsuccessful, clotting parameters generally improved and there was a significant decrease in requirement for blood products and crystalloids/colloids following rFVIIa administration.

Formal comparison of different anticoagulant therapies was not possible due to small patient numbers. However, it is noteworthy that amongst those who received LMWH, administration of rFVIIa was associated with cessation or decreased bleeding. This is of potential clinical benefit in view of the current absence of a reliable antidote to LMWH and the agent's long half-life. Protamine is commonly used to reverse the effects of UFH therapy, but is less reliable for LMWH.^[16] Clinical benefit was also seen in patients who had received UFH and/or coumarin. Our experience of reversing the effects of warfarin are supported by a study from Deveras and Kessler,^[19] who showed that rFVIIa successfully reversed the effects of excessive warfarin anticoagulation in 13 patients. In four of these patients who were actively bleeding, hemorrhage stopped immediately after rFVIIa administration. We note that a recent study favored continuous intravenous infusion of rFVIIa over intravenous bolus administration for patients deficient in Factor VII and undergoing surgery.^[20]

The dose required to achieve hemostasis varies according to different reports. For patients with hemophilia A or B, the typical dose of rFVIIa is in the range 90-110 $\mu\text{g}/\text{kg}$ every 2-3h until cessation.^[21] In the current study, a single dose of rFVIIa

was effective in all but one patient and at slightly lower dosages than those recommended for hemophilia (median dose: 87.35 $\mu\text{g}/\text{kg}$ body weight). In one subject (Patient 10), a small dose (20.0 $\mu\text{g}/\text{kg}$) proved sufficient to achieve hemostasis, a dose consistent with that recommended by some authors.^[22] In a series of 16 patients presenting with a major bleeding event concurrent with use of warfarin, a single dose of 1.2 mg of rFVIIa at $16.3 \pm 4.1 \mu\text{g}/\text{kg}$ normalized the INR in all patients and was clinically efficacious in 14 of 16 patients.^[23] It should be noted that patients included in the present study did not receive some of the latest generation of anticoagulants. Agents such as danaparoid sodium and fondaparinux, which predominantly or exclusively have anti-FXa activity, currently lack a specific antidote.

In this study, rFVIIa was well tolerated and no adverse events were reported. Whilst the mechanism of action of rFVIIa has not been fully elucidated,^[24] there is a potential risk of thromboembolic events.^[26-28]

Thus, the study suggests that rFVIIa can control severe bleeding in patients receiving a variety of anticoagulant therapies that is unresponsive to traditional antidotes. Additional benefits may include fewer side-effects compared to other haemostatic agents and in certain circumstances more cost-effective management (e.g., when compared to APCC). It is worthwhile to consider undertaking research to determine the efficacy and safety and define optimal dosing of rFVIIa in anticoagulated subjects.

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