Recombinant Factor VIIa in the Treatment of Postoperative Hemorrhage After Cardiac Surgery

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Background. **A generalized coagulation disorder after cardiac surgery that is associated with massive postoperative hemorrhage is not completely understood. Recombinant factor VIIa (rFVIIa) has emerged as a possible "salvage" medication. Limited experience reported in the literature and fears of possible thromboembolic complications make the use of rFVIIa in the treatment of bleeding after cardiac surgery controversial.**

Methods. **We analyzed retrospectively all consecutive cardiac surgical patients who have received rFVIIa in the Helsinki University Hospital in order to evaluate the safety and efficacy of rFVIIa after cardiac surgery in our institution. Altogether, 16 patients were identified from operating room and intensive care unit (ICU) databases. Patient records and operating room and ICU databases were reviewed.**

Results. **In this series of high risk patients hospital mortality was high (25%). A definite hemostatic effect was seen after rFVIIa administration in all but three patients (82%). Mean amount of bleeding and amount of platelet and fresh frozen plasma transfusions decreased significantly after rFVIIa administration. Four patients had serious postoperative thromboembolic complications.**

Conclusions. **Recombinant factor VIIa was effective in restoring hemostasis, but thromboembolic complications occurred after rFVIIa use. They may be related to the underlying pathologies and surgery performed. It is possible, however, that rFVIIa treatment contributed to their occurrence.**

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Recombinant factor VIIa (rFVIIa, NovoSeven, NovoNordisk, Bagsvaerd, Denmark) was developed for the treatment of bleeding in patients with hemophilia A and B who have inhibitors against factors VIII and IX, respectively. It has been used for this indication since 1988 and the incidence of treatment-related serious adverse events has been low (under 1%). The use of rFVIIa is approved by the United States Food and Drug Administration solely for this indication and all other use is therefore "off label" [1].

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However, successful treatment of bleeding in patients with other coagulopathies, such as congenital and acquired FVII deficiency, von Willebrand's disease, thrombocytopenia, and the platelet function defects Glanzmann's thrombasthenia and Bernard-Soulier syndrome, has also been reported [2]. Recombinant factor VIIa has also been used to treat bleeding in patients with apparently normal hemostasis prior to the bleeding episode [3]. The first report of the use of rFVIIa for the successful treatment of a life-threatening traumatic bleeding after a gunshot injury was published in 1999 [4]. After the report of treatment of two cases of massive intraabdominal postoperative hemorrhage with rFVIIa [5] other anecdotal reports of rFVIIa use for intractable postoperative bleeding have been published [2]. In a single small randomized trial with patients undergoing elective retropubic prostatectomy the prophylactic administration of low-dose rFVIIa reduced bleeding and transfusions [6].

A generalized coagulation disorder after cardiac surgery that is associated with massive postoperative hemorrhage is not completely understood. The use of rFVIIa after cardiac surgery has been controversial because there is a theoretical concern that giving rFVIIa after cardiac surgery and cardiopulmonary bypass in a situation of enhanced thrombin generation and tissue factor expression would be a risk for thrombotic complications [7]. However, rFVIIa has emerged as a possible "salvage" medication to treat intractable postoperative bleeding. The experience reported in the literature is based on a few case reports [8–14] and two small case series in pediatric cardiac surgical patients [15, 16] and two case series in adult cardiac surgical patients, the other of which is in abstract form [17, 18]. Thromboembolic complications have not been reported in any of these reports. However, a single fatal thrombosis after prothrombin complex concentrate and rFVIIa administration to a patient on extracorporeal membrane oxygenation with excessive bleeding after redo lung transplantation has been reported [19]. Because of the limited experience and controversy related to the use of rFVIIa in the treatment of bleeding after cardiac surgery, this study was undertaken to analyze all consecutive cardiac surgical patients

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Table 1. Patient Demographics

Patient No.	Age (Years)	Gender	EuroSCORE	EuroSCORE Logistic (%)	LVEF (%)	Hypertension	CAD	Diabetes mellitus	COPD	PAD	Renal Failure	Preoperative Neurologic Deficit
1.	47	Male	7	9.0	NA							
2.	71	Male	14	45.0	NA	Yes	Yes				Yes	
3.	77	Female	10	18.4	>60	Yes				Yes	Yes	
4.	69	Female	5	4.0	>60	Yes			Yes			
5.	60	Male	8	9.6	NA	Yes	Yes					Yes
6.	51	Male	8	12	>50	Yes						
7.	76	Male	16	59.5	NA	Yes		Yes				
8.	75	Male	11	22.4	NA							
9.	67	Male	15	53.7	NA	Yes				Yes		Yes
10.	72	Female	9	12.1	>50		Yes					
11.	51	Male	8	14.0	NA	Yes						
12.	45	Male	7	8.5	30							
13.	27	Male	7	8.6	60							
14.	52	Male	6	7.4	>60							
15.	28	Male	10	21.2	25							
16.	55	Male	8	11.1	20		Yes					
Mean (SD)	60 (14.9)		9.4 (3.2)	20.3 (17.3)								

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NA = not available; PAD = peripheral arterial disease; SD = standard deviation.

who have received rFVIIa in our institution and to evaluate the safety and efficacy of rFVIIa after cardiac surgery in our institution.

Material and Methods

From the operating room and ICU databases we identified retrospectively all consecutive cardiac surgical patients in the Department of Cardiothoracic Surgery of the Helsinki University Hospital, Helsinki, Finland who had received rFVIIa intraoperatively or postoperatively for intractable bleeding. Altogether, 16 such patients who were operated between May 31, 2002 and October 5, 2004 were identified from a total of approximately 2,800 cardiac surgery cases operated during the same time period. Patient records and operating room and ICU databases were reviewed to assess the efficacy and safety of rFVIIa treatment. To assess efficacy hourly bleeding volumes and data of blood products and other hemostatic agents administered 6 hours prior to and 6 hours after rFVIIa administration were registered. The clinical outcome and any reported thromboembolic complications were registered. The study was approved by the Institutional Review Board.

The operative risk was evaluated with the EuroSCORE scoring system, which takes into account several patient, cardiac, and operation related preoperative risk factors such as age, sex, the presence of pulmonary, neurologic, and renal comorbidity, the presence of extracardiac arteriopathy, previous cardiac surgery, active endocarditis, unstable angina, left ventricle dysfunction, recent myocardial infarct, pulmonary hypertension, urgency, and the type of surgery performed [20].

Patient care followed institutional guidelines during the study period. Cardiopulmonary bypass (CPB) was performed using a noncoated circuit and a membrane oxygenator. Heparin (5,000 IU) was added to the CPB priming solution and an initial intravenous dose of 300 IU/ kg of heparin was administered. Heparinization was monitored with kaolin-activated clotting time (ACT) measurements every 30 minutes and ACT was maintained above 480 seconds with additional doses of 5,000 IU of heparin intravenously if needed. Heparinization was neutralized with 1 mg of protamine sulphate per 100 IU of the heparin loading dose. During cardiopulmonary bypass hematocrit was maintained above 0.25. After CPB the cutoff values for postoperative packed red blood cell transfusions were hemoglobin under 80 g/L or hematocrit under 0.30. In case of increased intraoperative or postoperative bleeding (chest tube bleeding $>$ 200 mL/ hour) plasma-activated partial thromboplastin time, plasma thromboplastin time, and platelet count were measured. If plasma thromboplastin time was prolonged more than 1.5 fold from the preoperative value or plasma-activated partial thromboplastin time was over 50 seconds, 15 mL/kg of fresh frozen plasma was administered. If the platelet count was under 100×10^9/L, one unit of platelet concentrate/10 kg of weight was administered. Prothrombin complex concentrate, human factor VIII-von Willebrand factor concentrate, human fibrinogen concentrate, and factor XIII concentrate could be used as part of the component therapy administered according to the anesthesiologist's discretion. The use of rFVIIa was reserved for life-threatening bleeding with no identifiable surgical source after adequate, conventional blood component therapy as suggested in the literature

Table 2. Surgical Data

Patient No.	Diagnosis	Operation	Emergency	Redo	DHCA	Reexploration for bleeding	Antifibrinolytic therapy
1.	Acute type A aortic dissection	Composite graft	Yes		Yes	Yes	Tranexamic acid
2.	Acute rupture of descending thoracic aorta	Descending aortic reconstruction	Yes			Yes	
3.	Aneurysm of the ascending aorta, AI	Bioprosthetic AVR, reconstruction of the ascending aorta				Yes	Tranexamic acid
4.	Aneurysm of the ascending aorta, aortic stenosis	Mechanical AVR, Robiczsek support of the ascending aorta					Tranexamic acid
5.	Acute rupture of descending thoracic aorta, nonruptured abdominal aortic aneurysm	Reconstruction of the descending thoracic aorta, aortofemoral and aortoiliac reconstruction	Yes				Aprotinin
6.	Aneurysm of the aortic arch and descending thoracic aorta	Reconstruction of the aortic arch and descending thoracic aorta			Yes	Yes	
7.	Acute type A aortic dissection, cardiac tamponade	Reconstruction of the ascending aorta	Yes		Yes		Aprotinin
8.	Acute type A aortic dissection	Composite graft, femoro-femoral cross-over	Yes		Yes		Aprotinin
9.	Acute dissection and rupture of the aortic arch	Reconstruction of the aortic arch	Yes	Yes	Yes		Aprotinin
10.	Aortic stenosis, tricuspid valve insufficiency, CAD	Bioprosthetic AVR, tricuspid valvuloplasty, CABG		Yes			Aprotinin
11.	Acute type A aortic dissection	Reconstruction of the ascending aorta and the aortic arch	Yes		Yes		Tranexamic acid
12.	Hypertrophic obstructive cardiomyopathy	Heart transplantation	Yes				Aprotinin
13.	Acute aortic valvular endocarditis, AI	Mechanical AVR and reconstruction of the aortic annulus					Aprotinin
14.	Aneurysm of the ascending aorta	Composite graft					Aprotinin, Tranexamic acid
15.	Transposition of the great arteries	Heart and lung transplantation	Yes	Yes			Aprotinin
16.	Ischemic cardiomyopathy	Heart transplantation	Yes	Yes			Aprotinin

AI = aortic valve insufficiency; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DHCA = deep hypothermic circulatory arrest.

[3]. During the study period there were no institutional guidelines for the dosage of rFVIIa.

The data were analyzed with the SPSS for Windows release 11.5.1 software (SPSS Inc, Chicago, IL). Normality of distributions was tested with the Kolmogorov-Smirnov test. The Mann-Whitney *U* test was used when comparing bleeding and transfusions before and after rFVIIa administration. The p values of 0.05 or less were considered statistically significant.

Results

Demographic and surgical data of the patients are summarized in Tables 1 and 2. The mean age of the patients was 58 years (range, 27–77 years). None of the patients had a known coagulation defect preoperatively. The majority of cases were emergency operations (10 of 16). The patients operated were high risk patients (mean EuroSCORE 9.3, and mean logistic EuroSCORE expected risk of mortality 19.8%) and the surgery was complex in most of the cases. Six operations involved the use of deep hypothermic circulatory arrest and there were four redo cases. Most commonly a procedure involving either the ascending aorta, aortic arch, or descending thoracic aorta was performed (11/16). Either a dissection or acute rupture of the aorta was the indication for operation in nearly half of the cases (7/16). Reexploration for bleeding was performed in four cases. The clinical results are summarized in Table 3. Hospital mortality of the patients in this series was 25% (4/16). Mean intensive care unit stay was 21 days (range, 1–167 days). Several major complications that are not related to the use of rFVIIa occurred (Table 3).

The mean dose of rFVIIa used was 65 μg/kg (range,

Table 3. Clinical Outcome

Patient No.	Hemostasis After rFVIIa	Dose of rFVIIa (μg/kg)	ICU Stay (Days)	Death	Cause of Death	Other Major Complication	Thromboembolic Complication
1.	No	28	2	Yes	MOF	MOF	
2.	Yes	107	75	No		Hemodialysis, paraplegia	
3.	Yes	29	5	No			
4.	Yes	106	1	No			
5.	Yes	30	10	No		Hemodialysis, paraplegia	Acute thrombosis of left iliac artery, thrombosis of right aortoiliac graft limb
6.	Yes	58	18	No			
7.	Yes	87	25	No		Hemodialysis	Stroke, Multiple embolic cerebral infarcts
8.	Yes	24	167	No		Hemodialysis, critical illness polyneuropathy	Thrombosis of right iliac artery
9.	Yes	40	16	No		Hypoxic ischemic encephalopathy	
10.	Yes	42	4	No			
11.	Yes	NA	10	No		Transient paraplegia	
12.	Yes	43	0	Yes	Acute graft failure		Acute myocardial infarctions in the left ventricle
13.	Yes	37	3	No			
14.	Yes	100	5	No			
15.	No	192	1	Yes	Uncontrollable bleeding	MOF, graft failure	
16.	No	53	0	Yes	Uncontrollable bleeding	MOF, graft failure	

ICU = intensive care unit; MOF = multiorgan failure; NA = not available.

24–192 μg/kg) (Table 3). A definite hemostatic effect according to either the surgeon's or anesthesiologist's evaluation was seen soon after rFVIIa administration in all but three patients (82%). All of the patients who did not respond to treatment died of multiorgan failure subsequently. The postmortem examinations did not reveal any surgical source of bleeding in any of these three patients. In general rFVIIa administration resulted in a significant decrease in the mean amount of bleeding, when cumulative bleeding in all patients during the 6 hours prior to rFVIIa administration was compared to the cumulative bleeding during the 6 hours after rFVIIa administration (Table 4). The amount of platelet and fresh frozen plasma (FFP) transfusions decreased significantly after rFVIIa administration. There was no significant change in the amount of packed red blood cell (RBC) transfusions. Almost two thirds (10/16) of the patients had received aprotinin and almost a third (five patients) had received tranexamic acid during the 6 hours prior to rFVIIa administration. Only two patients had received no antifibrinolytic medication (Table 2). Five patients had received either human factor VIII-von Willebrand factor concentrate or human fibrinogen or both prior to rFVIIa administration. Only one patient, patient No. 15, who did not respond to rFVIIa treatment, had received human factor VIII-von Willebrand factor concentrate, human fibrinogen, antithrombin III, and prothrombin complex concentrate after rFVIIa administration in a desperate and unsuccessful attempt to restore hemostasis.

Table 4. Bleeding and Transfusions Before and After rFVIIa Administration

	6 Hours Before rFVIIa	6 Hours After rFVIIa	*p* Value
Bleeding (mL)	2180 (3520)	350 (620)	$p < 0.001$
Transfusions			
Platelets (units)	12 (20)	0 (8)	$p = 0.005$
Fresh frozen plasma (units)	3.0 (9.0)	1.0 (3.8)	$p = 0.017$
Packed red blood cells (units)	4.0 (4.8)	2.0 (5.0)	Not significant

Values are expressed as median and (interquartile range).

Four patients (25%) had severe postoperative thromboembolic or thrombotic complications (Table 3). Patient No. 5 was operated for acute rupture of an aneurysm of the descending thoracic aorta. He was also diagnosed with an unruptured infrarenal abdominal aortic aneurysm. The aneurysm of the descending thoracic aorta was reconstructed with a Dacron graft from a left thoracotomy under femoro-femoral cardiopulmonary bypass. Because of diffuse bleeding in the operative field, the patient received transfusions of packed RBCs, platelets, FFP, and 30 μg/ kg of rFVIIa. Hemostasis was achieved. Soon thereafter the left femoral artery became pulseless because of a thrombosis of the left iliac artery. A Y-graft reconstruction of the abdominal aortic aneurysm was performed with an aortofemoral anastomosis on the left side and an aortoiliac anastomosis to the left external iliac artery on the right side. Despite adequate heparinization thrombosis of the right graft limb was observed during suturing of the anastomosis. It was treated with thrombectomy of the graft limb. The postoperative course was complicated by paraplegia and acute renal failure that required hemodialysis.

Patient No. 7 was operated for acute type A aortic dissection. The ascending aorta was reconstructed with a Dacron graft leaving the aortic valve intact. The distal anastomosis was sutured under deep hypothermic circulatory arrest. There was increased bleeding into the chest tubes postoperatively and the patient received transfusions of packed RBCs, platelets, and FFP. The bleeding continued and the patient was given 87 μg/ kg of rFVIIa, which resulted in immediate hemostasis. The patient recovered otherwise, but was left with a left-sided paralysis and computed tomography scan of the brain showed multiple embolic infarctions bilaterally.

Patient No. 8 was operated for acute type A aortic dissection. The ascending aorta was reconstructed with a composite aortic mechanical valved graft. The distal anastomosis was sutured under deep hypothermic circulatory arrest. Diffuse bleeding was controlled with transfusions of packed RBCs, platelets, and FFP, and finally 24 μg/ kg of rFVIIa. Postoperatively the patient was diagnosed with acute ischemia of the right lower limb. Computed tomography angiography showed thrombosis of the right iliac artery and a left to right femoro-femoral cross-over was performed. The postoperative course was complicated by transient renal failure, critical illness polyneuropathy, and respiratory insufficiency, but after prolonged intensive care and rehabilitation the patient recovered and was discharged from the hospital.

Patient No. 12 received an orthotopic heart transplantation that was complicated by massive perioperative bleeding due to preoperative right side heart failure and liver failure. Bleeding stopped after transfusions of packed red cells, platelets, FFP, 3 g of human fibrinogen (Hemocomplettan®, Aventis Behring GmbH, Marburg, Germany), 1,000 IU of human factor VIII concentrate-von Willebrand factor concentrate (Haemate®, Aventis Behring GmbH, Marburg, Germany), and finally 43 μg/kg of rFVIIa. The immediate postoperative stage was stable until sudden acute graft dysfunction that led to resuscitation and emergency reinstitution of cardiopulmonary bypass occurred. The patient died despite circulatory support with bilateral centrifugal pumps. Histology of the transplanted heart showed multiple acute myocardial infarctions in multiple areas of the left ventricle.

Comment

In our series rFVIIa was effective in restoring hemostasis. However, several thromboembolic complications occurred after rFVIIa use. They are known complications of, especially, aortic and valve surgery and may be related to the underlying pathologies and the surgery performed. It is possible, however, that rFVIIa treatment contributed to their occurrence. Particularly, the case histories of patients Nos. 5 and 12 raise questions of the role of rFVIIa.

Predisposing factors, such as cardiovascular disease, atherosclerosis, hypertension, diabetes, or advanced age have been present in most of the patients who have suffered from thromboembolic complications after rFVIIa treatment [1, 2]. These risk factors are invariably present in cardiac surgical patients. Cardiopulmonary bypass causes activation of the hemostatic system and increased thrombin generation [21] and rFVIIa further enhances the rate of thrombin formation on activated platelets [2]. Tissue factor is expressed on atherosclerotic plaques and circulating tissue factor is present in patients with acute coronary syndromes [22]. Tissue factor is also expressed in ischemic myocardium [23]. Because, theoretically, rFVIIa acts at sites where tissue factor is exposed to the circulation, the administration of exogenous rFVIIa during tissue factor expression could be the cause of thrombosis.

Recombinant factor VIIa has a possible role in the treatment of otherwise intractable life-threatening bleeding after cardiac surgery, but randomized, controlled trials are required to prove its safety and efficacy. A prospective, randomized, placebo-controlled trial in adult cardiac surgical patients with a high risk of serious hemorrhage has been reported to being ongoing [24]. Based on our experience we recommend caution in the use of rFVIIa after cardiac surgery before the results of randomized trials are published. Furthermore, institutional guidelines to direct the use of rFVIIa after cardiac surgery should be established.

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