

Recombinant activated factor VII in the management of life-threatening bleeding in cardiac surgery

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Abstract

Objective: Massive perioperative bleeding is a potential complication of cardiac surgery, and may persist despite conventional interventions. rFVIIa is being increasingly used as additional therapy, and the aim of the present study was to describe our experience with rFVIIa in the management of life-threatening bleeding in adult cardiac surgery. **Methods:** Retrospective chart review of 24 patients undergoing a variety of cardiac procedures was performed at Sahlgrenska University Hospital between January and August 2004. The patients developed life-threatening bleeding during or after surgery despite conventional medical therapy and transfusion of blood products, and received rFVIIa as additional therapy. **Results:** rFVIIa was administered as a median bolus dose of 60 µg/kg. Nineteen patients received one dose of rFVIIa; the bleeding stopped or decreased in 18 of them. Five patients received repeated doses of rFVIIa. Fifteen patients were reexplored due to massive postoperative bleeding or cardiac tamponade and a surgical source of bleeding was identified in six of these patients. A statistically significant reduction in chest drain losses after administration of rFVIIa was demonstrated. No adverse reactions were noted. **Conclusions:** rFVIIa was successfully used as an additional therapy both during and after cardiac surgery, when bleeding was refractory to conventional methods. Bleeding stopped eventually in all patients and none of the patients exsanguinated.

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1. Introduction

Massive perioperative bleeding is a potential complication of any surgical procedure, and results in increased morbidity and mortality. Three to four percent of patients undergoing coronary artery bypass graft surgery (CABG) require reexploration for bleeding, which increases the mortality rate 2-3 times [1]. Perioperative bleeding may be caused by surgical factors or an impaired haemostasis. The bleeding of impaired haemostasis associated with cardiac surgery and the use of cardiopulmonary bypass is multifactorial. Both enhanced fibrinolysis, platelet dysfunction and coagulopathy secondary to the exposure of blood to artificial surfaces and the surgical trauma, have been implicated [2]. The increasing use of platelet inhibitors such as clopidogrel and thrombolytic therapy in patients with acute coronary syndrome and myocardial infarction may also be associated with bleeding problems if acute cardiac surgery is required [3,4]. Massive bleeding thus represents a major challenge to the surgeon and the anaesthesiologist; if uncontrollable, the patient will not survive.

Life-threatening bleeding may persist despite conventional medical therapy and transfusions. Activated factor VII is a naturally occurring initiator of haemostasis, and synthetic recombinant activated factor VII (rFVIIa) was originally developed for the treatment of bleeding in patients with haemophilia A or B with inhibitors to factor VIII or IX. At pharmacological doses, rFVIIa enhances the thrombin generation through direct activation of factor X, independent of the presence of factor VIII or IX [5]. rFVIIa has presented itself as a new tool in the management of critical haemorrhage associated with trauma and surgery in patients with previously normal haemostatic mechanisms [6]. A case report in 1999 described the first successful use of rFVIIa in the treatment of traumatic life-threatening bleeding [7]. There are only a few case reports describing the use and safety of rFVIIa in heart valve surgery and even less experience in CABG [8-13]. The aim of the present retrospective study is to review our experience with rFVIIa in the management of life-threatening bleeding in adult cardiac surgery.

2. Methods

2.1. Patients

A retrospective review was performed on the medical records of patients undergoing adult cardiac surgery at

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Table 1
Clinical details

Patient no.	Gender, age	Primary procedure	ECC (min)	Reexploration indication/finding	Second reexploration, indication/finding	rFVIIa	Dose ($\mu\text{g}/\text{kg}$)	Mortality after surgery
1, a	m 53	CABG	87	Tamponade/nsb		2	26	
2, a	f, 70	CABG		Tamponade/sb		2	87	
3, a	f, 70	CABG	155	Bleeding/sb	Bleeding/nsb	3	65	
4, a	m, 75	CABG	85	Bleeding/sb	Bleeding/nsb	3	32	
5, a	m, 42	CABG	166	Bleeding/sb	Tamponade/nsb	3	55	
6	m, 73	CABG	67	Bleeding/sb		4	19+19+38	
7	m, 65	CABG	51	Bleeding/nsb		4	60	
8	f, 60	CABG	75	Bleeding/nsb		2	76	
9	m, 73	CABG	46	Bleeding/nsb		2	32	
10, a	m, 60	CABG + aortic reconstruction	251	Tamponade/nsb		4	53+86	16 days
11	m, 82	CABG + AVR+TVR	177			1	67	2.5 months
12, a	m, 49	AVR + MVR	379	Tamponade/nsb	Bleeding/nsb	2,3,4	39+39+77+97+77	
13	m, 79	MVR + tricuspid repair	105	Tamponade/nsb		2	83+83	1 month
14	m, 66	MVR + tricuspid repair	210	Bleeding/nsb	Bleeding/nsb	3	66	
15	m, 45	AVR + mitral/tricuspid repair	398			1	30	3 days
16	m, 54	AVR	199			4	104	
17	m, 73	MVR	163			1	35	
18, a	m, 75	Aortic reconstruction	284			1	40	
19, a	m, 59	Aortic reconstruction	537			1	52	3 days
20, a	m, 52	Aortic reconstruction	196	Bleeding/sb		4	74	1 day
21	m, 34	Aortic reconstruction	125			4	45	
22, a	m, 58	Post infarction VSD	157			1	56	13 days
23	m, 38	ECMO removal				1	64	
24, a	m, 36	Heart transplantation	187	Tamponade/nsb		2	75+75	

a, acute operation; m, male; f, female; nsb, non-surgical bleeding; sb, surgical bleeding; rFVIIa administered at primary operation=1, at reexploration=2, at second reexploration=3, at postoperative ward=4.

Sahlgrenska University Hospital between January and August 2004, who received recombinant activated factor VII (rFVIIa, NovoSeven[®], Novo Nordisk, Bagsvaerd, Denmark) as an additional therapy for life-threatening bleeding. During the study period, 676 patients underwent open cardiac surgery. rFVIIa was administered to 24 patients, 21 males and 3 females, with a median age of 60 years (range 34-82 years), and a median weight of 75 kg (range 55-125 kg). Ten patients had on-going anticoagulant treatment; seven with aspirin, warfarin and/or dalteparin, three patients had received clopidogrel on the day of surgery and two of these were also treated with thrombolytic therapy. Patient characteristics are given in Table 1. There was no indication of a preoperative

haemostatic disorder; all patients had normal coagulation values, Table 2.

2.2. Haemostatic treatment

At our institution, conventional medical therapy to achieve haemostasis involves 2 g of tranexamic acid (Cyklo-capron[®]) at the start and at the end of operation, and protamine reversal of the effect of heparin after bypass to an activated clotting time of <130 s. In addition, predicted high-risk/complex procedure patients receive conventional full-dose aprotinin (Trasylol[®]) given as a 2 million units (U) loading dose and a 2 million U pump prime followed by 500.000 U/h. Sixteen of the 24 study patients received

Table 2
Laboratory and coagulation parameters

	Preoperative	Prior to rFVIIa	Postoperative
	<i>Normal range</i>		
Haemoglobin	132 (109-136)	103 (89-111)	105 (101-120)
Creatinine	113 (97-142)		141 (119-189)
ASAT	0.60 (0.40-1.0)		1.40 (0.90-3.20)
ALAT	0.60 (0.40-0.70)		0.50 (0.40-0.70)
Platelets	225 (170-305)	104 (71-137)	117 (84-192)
Fibrinogen		1.9 (1.4-2.2)	2.6 (2.5-3.3)
APTT	40 (36-46)	39 (39-70)	46 (35-51)
INR	1.1 (1.0-1.4)	1.4 (1.2-2.0)	0.9 (0.9-0.9)
ACT		150 (114-162)	122 (62-126)

ASAT, aspartate aminotransferas; ALAT, alanine aminotransferas; APTT, activated partial thromboplastin time; INR, international normalised ratio; ACT, activated clotting time. Postoperative samples were collected 05.00 day after surgery. Values are given as median and inter-quartile range.

aprotinin during the operation. Desmopressin was used occasionally.

In patients with bleeding unresponsive to conventional medical therapy and transfusions of fresh-frozen plasma and platelets, rFVIIa was used as an additional therapy. rFVIIa was administered as an intravenous bolus injection, which was repeated if massive bleeding continued. Acidosis and hypothermia were corrected before rFVIIa therapy. In addition, platelets were transfused and 2 g of fibrinogen were administered to all but four patients immediately before rFVIIa administration.

2.3. Statistical analysis

Data is presented as median and range or inter-quartile range, as appropriate. Bleeding during 2 h before and after administration of rFVIIa was compared using a Wilcoxon signed rank test for paired data. A P -value <0.05 was considered statistically significant.

3. Results

3.1. Cardiac procedures

Twenty-two of the 24 patients underwent cardiac surgery with cardiopulmonary bypass and one was operated off-pump. One patient with a left ventricular assist device (LVAD) and extracorporeal membrane oxygenation (ECMO) received rFVIIa at the operation when the ECMO system was removed. Further data are given in Table 1. Twelve operations were elective and twelve acute; nine were reoperations. The median operation time was 392 min (range 135-1080 min), the median cardiopulmonary bypass time was 164 min (range 46-537 min) and the median cross-clamp time was 80 min (range 25-285 min).

3.2. rFVIIa administration

The median time from onset of bleeding to administration of rFVIIa was 2 h. rFVIIa was given as an intravenous bolus injection of 60 $\mu\text{g}/\text{kg}$ (range 19.2-104 $\mu\text{g}/\text{kg}$). Nineteen patients received one dose of rFVIIa. Five patients received 2-5 bolus injections; the first and second patient received a dose of 4.8 mg that was repeated (75 and 82.8 $\mu\text{g}/\text{kg}$, respectively), the third received 4.8 and 7.8 mg (52.7 and 87.5 $\mu\text{g}/\text{kg}$), the fourth received three doses of 2.4, 2.4 and 4.8 mg (19.2, 19.2 and 38.4 $\mu\text{g}/\text{kg}$), and the fifth received five doses of 2.4, 2.4, 4.8, 6 and 4.8 mg (38.7, 38.7, 77.4, 96.8 and 77.4 $\mu\text{g}/\text{kg}$).

3.3. Bleeding

Bleeding stopped eventually in all patients and none of the patients exsanguinated. Fifteen patients (62%) were reexplored due to massive postoperative bleeding ($n=9$) or cardiac tamponade ($n=6$). A surgical source of bleeding was identified in six (40%) of these patients (Table 1). Five patients underwent a second reexploration due to diffuse bleeding ($n=4$) or cardiac tamponade ($n=1$), but no surgical source of bleeding was identified. rFVIIa was administered

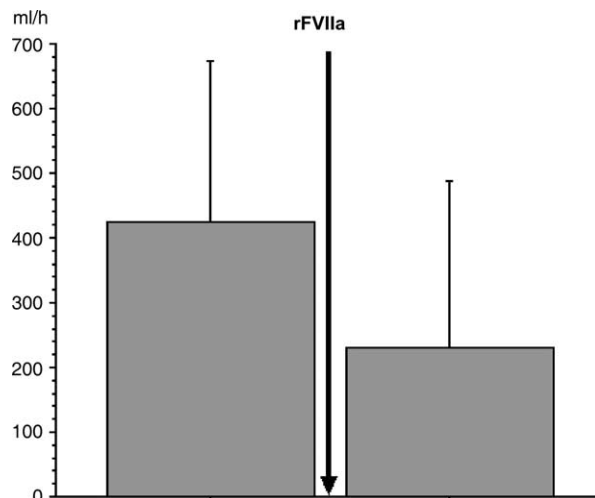


Fig. 1. Mean chest drain losses registered at the postoperative ward over 2 h before and after administration of rFVIIa in six patients at seven occasions. Values are presented as means \pm standard deviation. $P=0.018$.

to seven patients at the primary operation; none needed reexploration due to bleeding. Seven patients received rFVIIa at reexploration and in six of them the bleeding stopped. The seventh underwent a second reexploration due to massive bleeding and received additional doses of rFVIIa at the postoperative ward before the second reexploration, during the operation and postoperatively. Five patients received rFVIIa at the second reexploration. Seven patients were treated with rFVIIa in the postoperative care unit. One of them went to reexploration immediately after administration of rFVIIa, and a surgical source of bleeding was found. In six patients, it was possible to register chest drain losses at the postoperative ward over 2 h before and after administration of rFVIIa. Blood loss before and after rFVIIa administration was 424 ± 250 and 230 ± 259 ml, respectively ($P < 0.05$; Fig. 1).

3.4. Mortality

Overall, seven patients (29%) died between 1 day and 2.5 months after cardiac surgery. Two patients with aortic dissection died within 3 days after cardiac surgery, one due to ventricular fibrillation and the other died in cardiac arrest due to autopsy-confirmed dissection of the coronary arteries. All other deaths were caused by multiorgan failure.

4. Discussion

We have used rFVIIa as an additional therapy in 24 patients undergoing a variety of cardiac surgery procedures. The patients developed life-threatening bleeding during surgery or postoperatively despite conventional medical therapy and transfusion of blood products. Bleeding stopped eventually after administration of rFVIIa in all patients and none of the patients exsanguinated. A significant reduction in chest drain losses after administration of rFVIIa was demonstrated in six patients. There were no adverse reactions to rFVIIa.

There are two main causes of perioperative bleeding. The first is surgical bleeding, which is usually characterised by a single site of bleeding and confined to the operative site. The second, often more serious cause, is due to failure of the haemostatic pathways—non-surgical or haemostatic bleeding. Surgical trauma and cardiopulmonary bypass with contact between blood and the artificial surfaces of the bypass circuit may result in platelet dysfunction, haemodilution, activation of fibrinolysis, consumption of coagulation factors and hypothermia which may impair haemostasis [14,15]. Haemostatic bleeding is often evident as generalised oozing from the surgical wound already during the operation. Life-threatening postoperative bleeding may persist despite conventional medical therapy and transfusions, and reexploration may be required. However, reexploration may further worsen haemostasis and a surgical source of bleeding is found in far from all patients undergoing reexploration [16]. Although surgical bleeding is a subjective definition, in the present study we found a surgical source of bleeding at reexploration in only six out of 15 patients (40%).

rFVIIa may be a non-surgical tool that can contribute to control life-threatening peri- and postoperative bleeding. In the present series, rFVIIa was successfully used as an additional therapy in 24 patients, when bleeding was refractory to conventional methods. This is in accordance with previously published case reports [8-12]. Although there was a high mortality rate (29%), bleeding was never a direct cause of death. Nineteen patients received one dose of rFVIIa, the bleeding stopped or decreased in 18 of them and the 19th turned out to have a surgical bleeding at reexploration. Because this is a retrospective review, we cannot exclude that the reduction of blood loss may in part be due to a time difference. Five patients received repeated doses of rFVIIa, and it is possible that low initial doses administered to two of them (19 and 39 $\mu\text{g}/\text{kg}$) may have a sub-optimal effect on haemostasis. The minimal effective dose of rFVIIa, when used as a universal haemostatic agent, remains to be established. rFVIIa is supplied in vials of 1.2, 2.4 and 4.8 mg. Our doses were chosen with consideration of the vial sizes so that no drug was wasted. The median dose of rFVIIa used in our report is 60 $\mu\text{g}/\text{kg}$. This is lower than the doses recommended for treating bleeding in haemophilia patients with inhibitors, which is 90 $\mu\text{g}/\text{kg}$ [5]. A wide range of doses is used in severe bleeding in surgery and trauma. In previous reports of the use of rFVIIa following cardiac surgery, doses from 30 to 120 $\mu\text{g}/\text{kg}$ have been administered [8-12,17]. In a recently published retrospective study, 24 patients undergoing cardiac surgery, similar to our patients, were treated with rFVIIa administered as a bolus dose of 90 $\mu\text{g}/\text{kg}$ [13]. The overall mortality rate in that study was 75%; only 12 patients survived more than 4 h, but for those rFVIIa was shown to decrease blood product use.

Failure or delay to control massive bleeding will often lead to a combination of hypothermia, acidosis and coagulopathy, factors that continue to adversely affect haemostasis [17]. Consequently, it is essential for optimal haemostasis to correct or improve these factors. Transfusions should aim to correct coagulopathy before administration of rFVIIa [18,19]. In a situation with uncontrolled bleeding, events proceed at a fast and dramatic pace, therefore, it is important to be active and co-ordinate

intensive medical therapy. Before rFVIIa therapy in our patients, we aimed at a haemoglobin level of 100 g/l, recently transfused fresh-frozen plasma and platelets, and recently administered fibrinogen.

There were no adverse reactions to rFVIIa in our experience. However, rFVIIa is a prothrombotic agent and this has been raised as a concern when used in surgery that involves coronary arteries [20]. By enhancing the generation of thrombin on activated platelets, rFVIIa facilitates the formation of a stable fibrin clot [5]. This mechanism of action suggests that the effects are limited to the site of injury and that systemic activation of the coagulation cascade does not occur. The local effect of rFVIIa is supported in reports describing paediatric cardiac surgery, where there was no evidence of thrombotic occlusion of shunt or conduits following the use of rFVIIa [21]. There was no evidence of prothrombotic complications in an orthotopic heart transplant patient with the use of an intraaortic balloon pump in the immediate postoperative period [22]. In a large controlled clinical trial in 245 patients with upper gastrointestinal bleeding, thrombotic adverse events occurred with no greater frequency in patients receiving multiple 100 $\mu\text{g}/\text{kg}$ doses of rFVIIa than those receiving placebo [23]. Overall, thrombotic events after treatment with rFVIIa seem to be rare, and in many cases alternative aetiology was present such as the primary cause of the thromboses could not be determined [24,25].

In summary, we report a case series of 24 patients undergoing cardiac surgery complicated with life-threatening bleeding. rFVIIa was successfully used as an additional therapy alone or in combination with reexploration, when bleeding was refractory to conventional methods. However, the retrospective design of the study, the low number of patients and patient selection limit the conclusions. Several questions remain to be answered, e.g. what is the optimal time of administration of rFVIIa and what is the optimal dose. There is definitely a need for additional haemostatic therapies after cardiac surgery, and in high transfusion risk cases it may be used preventively. Randomised, controlled, multicenter clinical trials are required to prove its safety and efficacy in cardiac surgery, and to determine the indications for its use.

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