Effective Management of Refractory Postcardiotomy Bleeding With the Use of Recombinant Activated Factor VII

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Background. **Severe coagulopathy after cardiovascular surgery may lead to intractable bleeding and is associated with increased mortality and morbidity. Recent studies have suggested that recombinant activated factor VII (rFVIIa) may play a role in decreasing postoperative bleeding. Herein we report our experience with the off-label use of rFVIIa in patients with refractory postcardiotomy bleeding.**

Methods. **From June 2003 to December 2005, 17 patients (mean age, 65 ± 18 years) received rFVIIa for refractory bleeding after cardiac surgery. Preoperative risk factors for bleeding included reoperation (n = 7), emergency surgery (n = 7), and renal or hepatic failure (n = 3). Surgical procedures were aortic surgery (n = 7), complex valve operations (n = 7), coronary artery bypass grafting (n = 2), and cardiac tumor resection (n = 1).**

Results. **The average dose of rFVIIa was 103.1 ± 30.2 μg/kg. After the administration of rFVIIa the blood loss was reduced and chest tube output decreased from an average of 300 mL/h to 60 mL/h ($p = 0.024$). Coagulation variables normalized (mean prothrombin time, 18 ± 7 versus 14 ± 3 seconds; $p = 0.03$; mean partial thromboplastin time, 94 ± 50 versus 49 ± 14 seconds; $p = 0.02$), and the need for blood products was significantly reduced. Only 1 patient required mediastinal reexploration. No thromboembolic complications occurred during hospitalization.**

Conclusions. **This study suggests that rFVIIa is safe and efficacious in the management of refractory postcardiotomy bleeding. The use of rFVIIa is associated with reduced blood loss, rapid improvement of coagulation variables, and decreased need for blood products. Further studies are necessary to determine the safety and efficacy of this new hemostatic agent and its precise role in the treatment of severe postoperative coagulopathy.**

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Significant advances in perioperative medical management and surgical techniques have both contributed to decreasing the incidence of severe bleeding in patients undergoing cardiac surgery. Refractory bleeding secondary to severe coagulopathy, however, still occurs occasionally in patients undergoing complex cardiac procedures [1, 2]. The correction of this condition requires the administration of large amount of blood products, which has limited efficacy and is often associated with increased postoperative morbidities and mortality [2].

Recombinant activated factor VII (rFVIIa; NovoSeven, NovoNordisk, Copenhagen, Denmark) is a hemostatic agent that was initially developed for the treatment of bleeding in patients with hemophilia A or B with inhibitors to factor VIII and IX [3, 4]. More recently, the off-label use of this agent was reported in patients with life-threatening bleeding after trauma or major abdominal surgery [5, 6]. The use of rFVIIa is not well-known in cardiac surgery, and only a few case reports [7, 8] or series [9–13] have reported its use and safety in this patient population. Herein we report our clinical experience in patients who were treated with rFVIIa for intractable bleeding after cardiac surgery at our institution.

Material and Methods

We conducted a retrospective review of 17 patients who underwent cardiac surgery at Mount Sinai Medical Center between June 2003 and December 2005 and received rFVIIa for refractory bleeding (off-label use). Recombinant activated factor VII was administered to all patients because of the persistence of major life-threatening bleeding after the completion of cardiopulmonary bypass and after the administration of large amount of blood products. A thorough medical chart review was performed to collect preoperative, intraoperative, and postoperative variables. The protocol was approved by our local institutional review board, including a waiver of informed consent, and was compliant with the Health Insurance Portability and Accountability Act of 1996 regulations.

Patient Characteristics

The demographics and clinical characteristics of the 17 patients are reported in Table 1. Mean age in this

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Table 1. Demographics and Preoperative Risk Factors

Patient	Age/Sex	Pathology	EF	Priority	Other Risk Factors
1	82/M	CAD, PTCA failure	0.46	Emergent	PTCA failure, MI, HIT
2	87/F	MR, TR, CAD	0.60	Urgent	Pulmonary edema
3	58/M	Dissection type A	0.60	Emergent	Acute paraplegia, RRF
4	74/F	MR, TR	0.60	Elective	
5	45/M	Dissection type A	0.66	Emergent	Reoperation, Marfan's syndrome
6	81/F	CAD, PTCA failure	0.55	Emergent	PTCA failure, MI
7	48/M	Acute aortic endocarditis	0.25	Urgent	Liver cirrhosis (child B)
8	39/M	Dissection type A	0.25	Emergent	Lower limbs ischemia, rhabdomyolysis
9	79/F	Dissection type A	0.40	Emergent	Stroke, COPD, PV
10	49/M	Acute aortic endocarditis	0.50	Urgent	Reoperation, stroke, RRF, acute RF, dialysis
11	83/F	AS, MR, CAD	0.11	Elective	
12	58/M	RV carcinoma, TR	0.60	Urgent	
13	84/M	Aortic aneurysm	0.70	Emergent	Reoperation aneurysm rupture
14	29/M	AS, MR, TR	0.20	Elective	Reoperation, Marfan's syndrome
15	63/M	Aortic aneurysm	0.50	Elective	Reoperation
16	70/M	MR, TR	0.50	Urgent	Reoperation, stroke, liver cirrhosis (child B)
17	81/F	Aortic aneurysm	0.40	Elective	Reoperation

AS = aortic stenosis; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HIT = heparin-induced thrombocytopenia; MI = myocardial infarction; MR = mitral regurgitation; PTCA = percutaneous transluminal coronary angioplasty; PV = polycythemia vera; RF = renal failure; RRF = respiratory failure; RV = right ventricle; TR = tricuspid regurgitation.

population was 65 ± 18 years. Eleven (65%) patients were male. Mean ejection fraction was 0.46 ± 0.17. Mean body weight and body surface area were 90 ± 44.1 kg and 1.4 ± 0.5 m^2, respectively.

The distribution of preoperative risk factors for bleeding is also reported in Table 1. Seven (41%) patients underwent reoperative procedures. Seven (41%) patients underwent surgery on an emergent basis. Two (12%) patients presented with acute aortic endocarditis. Acute renal failure and liver cirrhosis (child B) were present in 1 and 2 patients, respectively. The 2 patients who underwent emergent coronary artery bypass grafting were taking aspirin, abciximab, clopidogrel, and bivalirudin preoperatively. Finally, 1 patient presented with polycythemia vera.

Additional preoperative risk factors included recent stroke (n = 3, 18%), respiratory failure requiring intubation (n = 2, 12%), and acute myocardial infarction (n = 2, 12%). Finally, 2 patients required preoperative cardiopulmonary resuscitation.

Intraoperative Hemostatic and Anticoagulation Management

After induction of general anesthesia, a loading dose of ε-aminocaproic acid (150 mg/kg) was administered for 30 minutes, followed by a continuous infusion of 15 $mg \cdot kg^{-1} \cdot min^{-1}$. No ε-aminocaproic acid was added to the cardiopulmonary bypass circuit prime. The infusion was continued until the end of surgery. Seven (41%) patients in this study were given ε-aminocaproic acid.

Aprotinin was administered at a loading dose of 2,000,000 KIU intravenously for a 30-minute period. After completion of the loading dose, a maintenance dose of 500,000 KIU was started and continued until the surgical procedure was finished. In addition 2,000,000 KIU was added to the cardiopulmonary bypass circuit prime. Ten (59%) patients received aprotinin intraoperatively.

Before establishment of cardiopulmonary bypass heparin was given to achieve an activated clotting time of at least 480 seconds with a heparin level at or greater than 200 U/kg, or more specifically 2.7 U/mL circulating volume. After the completion of cardiopulmonary bypass, protamine was given on the basis of the heparin level.

After the administration of protamine, blood products (packed red blood cells, fresh-frozen plasma, platelets, and cryoprecipitate) were given to correct the coagulopathy. In the absence of response to transfusion, rFVIIa was administered as a "last resort" therapy to control the bleeding. The timing of administration was determined on an individual basis by the surgical and intensive care unit team.

Complete coagulation profile was obtained in all patients at the following time points: preoperatively, before the administration of rFVIIa, and within 6 hours after its delivery. Information with respect to blood product transfusion was also obtained in all patients before and after the administration of rFVIIa.

Surgical Procedures

Seven (41%) patients had aortic operations (2 ascending aorta and arch replacement, 1 extensive thoracoabdominal aneurysm repair, and 4 type A dissection repair). Two patients presented with Marfan's syndrome. The surgical repair required deep hypothermic circulatory arrest in 5 of these patients.

Table 2. Surgical Procedures and Recombinant Activated Factor VII Dosage

Patient	Primary Procedure	Intraoperative Findings/Comments	CPB (min)	rFVIIa (μg/kg)
1	CABG	LAD rupture, tamponade, extensive epicardial hematoma	127	68.9
2	MVR, TVP, CABG, aortic replacement	Aortic root and mitral annular calcification	576	103.4
3	Type A dissection repair	Tamponade, DHCA	338	106.6
4	MVR, TVP	Mitral annular hematoma	483	111.6
5	Thoracoabdominal aneurysm repair		219	87.7[a]
6	Off-pump CABG	RCA dissection Extensive epicardial hematoma	0	80[a]
7	AVR		120	112[a]
8	Type A dissection repair	DHCA	420	128[a]
9	Type A dissection repair	DHCA	168	80[a]
10	Bentall	Large annular abscess	205	100
11	MVP, CABG, AVR, aortic replacement	Aortic root calcification	314	80
12	TVP, PVR, tumor resection	Extensive RVOT reconstruction	500	91.1
13	Aortic repair	Contained rupture	186	80
14	Bentall, TVP, MVP	Aortic root calcification	330	182.2
15	Bentall trifurcated graft	DHCA	405	90.0
16	MVR, TVP		216	84.2
17	Arch replacement, trifurcated graft	DHCA	190	168.4

[a] rFVIIa given in the intensive care unit.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; DHCA = deep hypothermia circulatory arrest; LAD = left anterior descending; MVR/P = mitral valve replacement/plasty; PVR = pulmonary valve replacement; rFVIIa = recombinant activated factor VII; RVOT = right ventricle outflow tract; TVP = tricuspid valve plasty.

Two (12%) patients underwent emergent coronary artery bypass grafting after failed percutaneous transluminal coronary angioplasty. These 2 patients presented with tamponade and extensive epicardial hematoma as a result of coronary artery dissection or perforation. Seven (41%) patients underwent multiple valve operations. Three of these patients had extensive aortic root calcification. Finally, 1 patient underwent the resection of a large right ventricle and pulmonary artery tumor necessitating an extensive right ventricular outflow tract reconstruction. The cardiac procedures and intraoperative findings are reported in Table 2. The mean cross-clamp time and bypass time were 196 ± 87 minutes and 282 ± 156 minutes, respectively.

Table 3. Blood Products[a]

Blood Products	Before rFVIIa Administration (n = 17)	After rFVIIa Administration (n = 17)	*p* Value
Red blood cells (units)	5.875 ± 4.98	2.46 ± 1.99	0.010
Fresh-frozen plasma (units)	6.93 ± 4.31	2.26 ± 1.62	0.001
Platelets (units)	17.1 ± 7.10	5.1 ± 5.14	0.001
Cryoprecipitate (units)	22.3 ± 18.4	5.73 ± 10.35	0.009

[a] Cryoprecipitate = 10 mL/U, fresh-frozen plasma = 250 mL/U, platelets = 50 mL/U, red blood cells = 250 mL/U.

Statistics

Values are expressed as mean ± standard deviation or as a percentage. Comparison between groups was performed with the use of analysis of variance, Student's *t* test, or the χ^2 test as appropriate. Statistical significance was considered when a probability value was less than 0.05.

Results

Recombinant activated factor VII was administered as a bolus intravenously during a 15-minute period. The average dosage of rFVIIa was 103 ± 30 μg/kg (Table 2). In 3 patients (patient 3, 14, and 17) a second dose of rFVIIa was administered because of persistent coagulopathy and active bleeding.

Twelve (70%) patients received rFVIIa in the operating room, whereas 5 (30%) patients had rFVIIa in the intensive care unit. Before the administration of rFVIIa, the average transfusion was 5.8 ± 4.9 units of packed red blood cells, 6.9± 4.3 units of fresh-frozen plasma, 17.1 ± 7 units of platelets, and 22.3 ± 18 units of cryoprecipitate (Table 3). Despite the administration of blood products, the coagulation profile remained abnormal in all patients (Table 4).

After the administration of rFVIIa, coagulation variables significantly improved with the correction of prothrombin time and partial thromboplastin time (Table 3). In parallel, blood loss significantly decreased, and the

Table 4. Coagulation Profile

Variable and Normal Range	Baseline (n = 17)	Before rFVIIa (n = 17)	After rFVIIa (n = 17)	*p* Value[a]
PT (s) 11.5–14.5	16.9 ± 4.1	18.1 ± 7.6	14.5 ± 3.0	0.030
INR ≤1.2	1.6 ± 0.7	1.9 ± 0.9	1.2 ± 0.3	0.037
APTT (s) 21.7–34	40.5 ± 10.2	95.3 ± 50.2	49.9 ± 14.0	0.003
ACT (s) 82–152	140.1 ± 30.9	173.1 ± 51.6	130.1 ± 10.6	0.037
Platelets ($10^3/\mu L$) 150–450	225.1 ± 142.8	140.3 ± 80.3	200.6 ± 95.7	0.027
Fibrinogen (mg/dL) 175–430	392.1 ± 184.6	246.6 ± 61.7	328.3 ± 134.8	0.004
Hemoglobin (g/dL) 13.9–16.3	12.6 ± 1.7	10.2 ± 1.5	12.5 ± 1.9	0.001
Hematocrit (%) 42–55	38.1 ± 5.9	28.6 ± 4.4	34.2 ± 4.2	0.001

[a] Estimated between values from the columns before rFVIIa and after rFVIIa.

ACT = activated clotting time; APTT = activated partial thromboplastin; INR = international normalized ratio; PT = prothrombin time; rFVIIa = recombinant activated factor VII.

need for transfusion of blood products was reduced in all patients with an average of 2.4 ± 2 units of packed red blood cells, 2.2 ± 1.6 units of fresh-frozen plasma, 5.1 ± 5 units of platelets, and 5.7 ± 10 units of cryoprecipitate (Table 3). In patients who received rFVIIa in the intensive care unit, the average chest tube drainage decreased from 300 mL/h to 60 mL/h ($p = 0.02$). Only 1 patient required mediastinal reexploration after rFVIIa administration for evacuation of a large mediastinal clot.

No thromboembolic events occurred in this series after rFVIIa delivery. The in-hospital mortality was 29% (n = 5). The causes of death were myocardial failure (n = 1, patient 2), extensive cerebrovascular accident (n = 2, patients 3 and 5), and multisystem organ failure (n = 2, patients 8 and 11). The 2 patients with postoperative stroke suffered from an intimal flap occluding the left carotid artery after acute type A aortic dissection. This diagnosis was made after a postmortem autopsy in both patients, which also ruled out any intracerebral thrombus formation. The patient with myocardial failure was an 84-year-old woman who underwent a complex valve procedure with prolonged cardiopulmonary bypass and cross-clamp time. She had intractable right ventricular myocardial failure despite inotropic support and intraaortic balloon pump insertion. Finally, the 2 patients who died of multisystem organ failure had a prolonged postoperative low cardiac output syndrome.

Postoperative morbidities included respiratory failure (n = 1), low cardiac output requiring intraaortic balloon pump insertion (n = 1), and sternal wound infection (n = 1).

Comment

Activated factor VII (FVIIa) plays a key role in the initiation of coagulation. After tissue injury, FVIIa becomes highly bound to tissue factor on the subendothelial cells. The tissue factor–FVIIa complex transforms factors IX and X into their active forms (FIXa, FXa), leading to the initiation of the coagulation cascade and ultimately thrombin generation and clot formation [8, 14]. The restoration of normal coagulation factors after the administration of rFVIIa affects both a prolonged prothrombin time and partial thromboplastin time. The correction of partial thromboplastin time is probably explained by the direct activation of factor X by rFVIIa [15].

Taking into consideration the hemostatic effect of this agent, rFVIIa has been recently used in the management of postoperative bleeding. The data with respect to the use of this agent in adult cardiac surgery are scarce and include often small observational case series [9–12]. Hyllner and colleagues [10] reported the use of rFVIIa in a series of 24 cardiac surgery patients with refractory bleeding. In this series, after the administration of a median bolus dose of 60 μg/kg, blood loss significantly decreased and coagulation variables were effectively corrected. In a case series of 9 patients, Halkos and coworkers [9] reported the use of rFVIIa as a rescue therapy for the control of postoperative bleeding. These authors also reported that the use of rFVIIa was associated with improved hemostasis and rapid reduction of blood loss, no need for surgical reexploration, and reduction of transfusion requirements. Our results confirm the findings of these two studies using rFVIIa in adult cardiac surgery patients. The administration of rFVIIa was associated with rapid normalization of coagulation variables and decreased blood loss. In this life-threatening condition, the use of rFVIIa was a very useful adjunct to control refractory postcardiotomy bleeding. No patients in our series died of this complication. Furthermore, despite the risk of hypercoagulable state induced by rFVIIa, no thromboembolic complications occurred in these 17 patients.

Similarly in a propensity score-matched case control study of 51 patients, Karkouti and associates [13] reported a markedly decreased blood loss and a reduced need for blood products after rFVIIa administration. These authors reported a similar rate of adverse events between the group of patients treated with rFVIIa and the matched control group, except for a higher rate of renal dysfunction in the rFVIIa group. It should be emphasized that the sample size was not large enough to detect significant differences between the two groups.

Our series presents several limitations similar to the studies reported by Hyllner and colleagues [10] and Halkos and associates [9]. First, this was a retrospective study; therefore, any conclusions should be limited in their implications. Second, the lack of a control group makes difficult any definite conclusions because the administration of rFVIIa did not occur in a random manner. Third, the lack of a precise and standardized protocol in terms of indications, timing, and dosage in the administration of rFVIIa as a rescue therapy for life-threatening bleeding render impossible any specific recommendations at the present time. Despite all these limitations, the accumulation of information through these retrospective studies is crucial in the future design of appropriate prospective studies.

In summary, these early promising results should be confirmed by additional studies to further determine the safety and efficacy of rFVIIa as a hemostatic agent in this particular indication. In addition, these studies should also address the questions of timing, dosage, and cost-effectiveness associated with the usage of this drug.

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