CARDIOVASCULAR

Early Experience With Activated Recombinant Factor VII for Intractable Hemorrhage After Cardiovascular Surgery

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Background. **Intractable hemorrhage after complex cardiovascular operations is a serious and potentially lethal complication. We report our experience with the use of activated recombinant factor VIIa (rFVIIa) as rescue therapy for patients with refractory postoperative hemorrhage.**

Methods. **From April 2002 through December 2003, 9 patients received rFVIIa for intractable hemorrhage after cardiovascular surgery. Patients underwent aortic surgery (2), coronary artery bypass graft surgery (4), double valve operations (2), and mitral valve replacement (1). Four of these procedures were reoperations. Intraoperative aprotinin was used in all patients. All patients underwent standard heparinization (300 IU/kg) before cardiopulmonary bypass and reversal with protamine.**

Results. **Five patients underwent reexploration for mediastinal hemorrhage before treatment; 2 were reexplored twice. The average transfusion requirement before rFVIIa administration was 9 U of blood, 7 U of plasma, 22 U of platelets, and 19 U of cryoprecipitate. rFVIIa was administered as an intravenous bolus at 68 to 120 μg/kg. Mean time of administration from the first operation was 10.9 ± 7.2 hours. At the time of activated rFVIIa administration, chest tube drainage averaged 640 mL/h. In all patients, chest tube drainage was dramatically reduced to less than 100 mL/h within 5 hours after drug delivery. None of the patients required reexploration after treatment. There were no postoperative neurologic or cardiovascular complications.**

Conclusions. **When used as rescue therapy for intractable hemorrhage after cardiovascular surgery, rFVIIa may be effective in promoting hemostasis, preventing reexploration, and reducing transfusion requirements.**

(Ann Thorac Surg 2005;79:1303–6)

Intractable hemorrhage is a dreaded complication after cardiovascular surgery that often requires reexploration and the administration of large quantities of blood products. The increased postoperative morbidity and mortality associated with excessive bleeding (> 2L) is partially related to the massive transfusion of blood products [1]. Currently available systemically administered agents that promote hemostasis include serine protease inhibitors (eg, aprotinin), antifibrinolytics, and desmopressin; however, these agents may not be effective in all cases.

Activated recombinant factor VII (rFVIIa) (NovoSeven, NovoNordisk, Copenhagen, Denmark) has been shown to be safe and effective in patients with hemophilia who have inhibitors to factors VIII or IX and is indicated for the prevention of perioperative or spontaneous hemorrhage in these patients [2]. Here, we report our early experience using rFVIIa as postoperative rescue therapy for cardiovascular surgery patients with intractable coagulopathy and hemorrhage despite reexploration, massive transfusion of blood products, and currently available hemostatic agents.

Material and Methods

From April 2002 through December 2003, 9 patients were treated with rFVIIa for refractory bleeding after cardiovascular surgery. Two patients had aortic operations, 4 had coronary artery bypass surgery, 2 had double valve operations, and 1 had a mitral valve replacement. Four of these procedures were reoperations.

Aspirin (81 mg) was administered the day before surgery in all patients undergoing coronary artery bypass graft surgery. None of the other patients undergoing valve or aortic surgery received aspirin the day before surgery; only

Dr Levy discloses that he has a financial relationship with NovoNordisk.

This article has been selected for the open discussion forum on the CTSNet Web Site:
http://www.ctsnet.org.discuss

Accepted for publication Sept 20, 2004.

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Published by Elsevier Inc

0003-4975/05/$30.00
doi:10.1016/j.athoracsur.2004.09.034

Table 1. Preoperative Hematologic Profile

Patient	Procedure	PT (seconds)	INR	PTT (seconds)	Platelets ($10^3/\mu L$)	ACT pre-CPB (seconds)
1	Asc. aortic aneurysm repair	14.0	1.09	29.3	91	140
2	Redo-redo CABG	12.4	0.93	32.8	379	153
[a]3	CABG	13.8	1.07	29.5	127	167
[a]4	Redo-redo MVR	16.7	1.35	35.1	190	189
5	Redo CABG	13.1	0.97	32.6	275	127
6	CABG	14.0	1.06	37.9	215	157
7	Redo aortic root replacement	14.1	1.10	49.0	179	171
8	Emergent MVR/TVR	17.3	1.41	39.4	263	92
9	MVrep/TVrep/RFA	12.6	0.97	26.3	105	135

[a] Patients 3 and 4 had been treated with warfarin, which was discontinued at least 3 days prior to surgery.

ACT pre-CPB = activated clotting time before cardiopulmonary bypass and systemic heparinization; CABG = coronary artery bypass grafting; INR = international normalized ratio; MVR = mitral valve replacement; MVrep = mitral valve repair; PT = prothrombin time; PTT = partial thromboplastin time; RFA = radiofrequency ablation; TVR = tricuspid valve replacement; TVrep = tricuspid valve repair.

one (patient 4) was taking daily aspirin (81 mg), which was withheld the day before surgery (Table 1). In addition, patient 2 was receiving clopidogrel, which was discontinued 7 days before surgery. Two patients had been treated with warfarin preoperatively, but their medication was discontinued at least 3 days before surgery. Preoperative coagulation and platelet profiles are listed in Table 1.

Intraoperative aprotinin was administered to all patients as a loading dose (2 million U), followed by a pump prime of 2 million U and 500,000 U/h. All patients underwent standard heparinization (300 IU/kg) before cardiopulmonary bypass that was monitored by activated clotting times and reversed with protamine sulfate (3 mg/kg). All patients undergoing coronary artery bypass graft surgery were scheduled to receive aspirin (81 mg) within 4 hours after surgery if chest tube drainage was less than 100 mL/h. However, the chest tube output in these patients was greater than 100 mL/h, so none of them received this postoperative dose.

Table 2. Number of Units of Blood Products Administered Prior to rFVIIa Administration

Patient	Prbcs	FFP	Platelets	Cryoprecipitate
1	6	4	16	10
2	6	6	16	20
3	12	6	32	20
4	17	6	32	10
5	6	6	8	10
6	9	8	32	20
7	10	12	32	40
8	8	8	16	30
9	8	4	10	10

Packed red blood cells, aprotinin, fresh frozen plasma, platelets, and cryoprecipitate transfusions listed were administered prior to rFVIIa administration.

Cryo = cryoprecipitate; FFP = fresh frozen plasma; Plts = platelets; Prbcs = packed red blood cells.

Results

Five patients were reexplored for mediastinal hemorrhage before rFVIIa administration; 2 patients were reexplored twice. In none of these patients was a surgical source for bleeding identified. The average transfusion requirement was 9 U of packed red blood cells, 7 U of plasma, 22 U of platelets, and 19 U of cryoprecipitate before the administration of rFVIIa (Table 2). Desmopressin was also administered to the patient with chronic renal insufficiency. Three patients received an additional dose of aprotinin (1 million U) before rFVIIa administration. The main indication for reexploration in these patients was continued bleeding in the absence of a significant coagulopathy (Table 3).

In those patients that did not undergo reexploration, diffuse microvascular bleeding was observed intraoperatively and excessive postoperative hemorrhage was anticipated. In this series, rFVIIa was administered as rescue therapy only after attempts to control catastrophic hemorrhage by blood product transfusion or reexploration to exclude surgical causes of bleeding failed. Al-

Table 3. Coagulation, Fibrinogen, and Platelet Profiles Obtained 1 to 6 Hours Prior to rFVIIa Administration

Patient	PT (sec)	INR	PTT (sec)	Fibrinogen (mg/dL)	Platelets ($10^3/\mu L$)
1	14.3	1.12	39.2	372	102
2	17.1	1.39	41.9	209	123
3	11.5	0.85	31.4	333	113
4	16.7	1.35	35.1	216	126
5	12.3	0.89	41.1	220	169
6	12.5	0.91	34.9	221	207
7	17.3	1.41	69.0	. . .	129
8	18.0	1.49	44.7	. . .	236
9	11.4	0.84	44.4	292	142

INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

Table 4. Need for Reexploration, Dosing and Timing of rFVIIa Administration, and Outcome

Patient	Reexplore	Dose (mg)	2nd dose (mg)	Timing of Drug Delivery (hours postop)	Outcome
1	No	4.8	No	1	discharge home
2	Yes	7.5	No	24	discharge home
3	No	4.8	No	5	discharge home
4	Yes × 2	2.4	2.4	19	discharge home
5	No	4.8	No	5	discharge home
6	Yes	4.5	4.5	12	died POD 2 (MSOF)
7	Yes	9	No	12	discharge to rehab
8	No	6	No	12	discharge home
9	Yes × 2	4.8	No	8	died POD 34 (sepsis)

Doses represent actual amount of rFVIIa delivered.

MSOF = multi-system organ failure; POD = postoperative day.

though protocols for rFVIIa administration in cardiovascular surgical patients have not been defined, we considered rFVIIa administration in patients with ongoing hemorrhage despite either reexploration or the administration of 16 U of platelets, 4 U of plasma, and 10 U of cryoprecipitate.

Recombinant FVIIa was administered as a single intravenous bolus over 15 minutes at 68 to 120 μg/kg (4.8 to 9 mg) or divided into 2 doses with the second bolus given within 1 hour after the initial bolus (Table 4). There were no additional infusions after the bolus treatments. Mean time of administration of rFVIIa from the first operation was 10.9 $\pm$ 7.2 hours. At the time of rFVIIa administration, chest tube drainage averaged 640 mL/h (Fig 1). In all patients, chest tube drainage was dramatically reduced to less than 100 mL/h within 5 hours after administration. Post-rFVIIa transfusion requirements were modest, with an average of 3 U of packed red blood cells and 2 U of plasma administered to correct anemia and coagulopathy. None of the patients required reexploration after the rFVIIa was administered.

Two in-hospital deaths occurred, one because of multisystem-organ failure and the other because of overwhelming sepsis. There were no incidences of post-

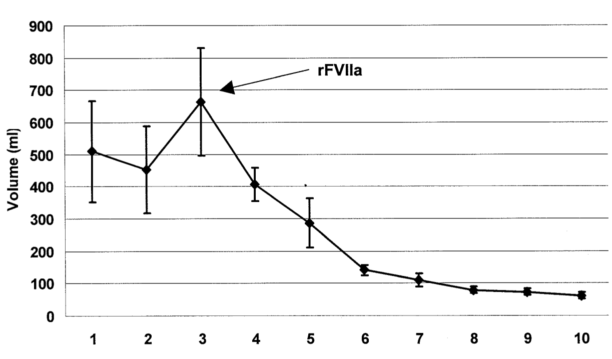

*Fig 1. Graph of chest tube drainage over time. After the administration of recombinant factor VIIa (*rFVIIa, arrow*), chest tube drainage was dramatically reduced within 5 hours to less than 100 mL/h. Data are expressed as mean ± standard error of the mean.*

operative myocardial infarction, stroke, or other thromboembolic complications. Seven patients recovered and were discharged.

Comment

Despite a more thorough understanding of risk factors associated with excessive bleeding after cardiovascular surgery, intractable postoperative hemorrhage remains a risk for patients with complex operations, prolonged cardiopulmonary bypass time, excessive intraoperative hemorrhage, reoperative procedures, and blood coagulation or platelet defects [3]. Allogeneic blood or blood product transfusion in cardiovascular surgical patients with excessive bleeding has been associated with increased morbidity and mortality [1]; therefore, reducing the incidence and severity of intractable hemorrhage has the potential to significantly improve outcomes and resource utilization in these patients.

Success with the use of rFVIIa in patients with hemophilia and inhibitors to Factors VIII and IX has resulted in the application of this agent in other settings of uncontrollable hemorrhage related to postsurgical coagulopathy. Different mechanisms have been reported for rFVIIa, including improved local hemostasis by initiating thrombin generation by binding to tissue factor at sites of injury and reversing platelet dysfunction [4, 5].

Although several case reports document the use of rFVIIa in bleeding cardiovascular surgical patients, our study represents a systematically reviewed series of adult cardiovascular surgical patients treated with rFVIIa for life-threatening hemorrhage. These patients were administered rFVIIa as rescue therapy only after other potential interventions and therapies were exhausted. In only 1 patient was rFVIIa administered within an hour after surgery; in this case, the patient was bleeding profusely (800 mL in the first hour) upon chest closure after an emergent ascending aortic aneurysm repair despite massive transfusion of blood products and aprotinin therapy. The response to rFVIIa administration was dramatic in all patients who received it, with prompt reduction in chest tube drainage and a reduction in further transfusion requirements. No patient required reexploration following the administration of rFVIIa and no thromboembolic complications occurred.

The optimal dose in cardiovascular surgical patients has not been determined, but we used the dosing regimen for hemophiliac patients (90 μg/kg) as a reference. Our range of dosing reflects the lack of a standardized dosing regimen for these patients. However, we have previously reported successful hemostasis in Jehovah's Witness patients with the lower doses [6].

Despite questions [7] regarding the use of this agent in cardiovascular surgery patients, intractable hemorrhage remains an important problem for cardiac surgeons. Safety regarding the use of a prohemostatic agent in patients with diffuse arteriosclerosis (especially patients undergoing coronary surgery) must be addressed.

Hospital costs may be cumbersome. rFVIIa is packaged in vials of 1.2, 2.4, and 4.8 mg. At $850 per mg of rFVII administered, the cost to the Emory Crawford Long Hospital, Atlanta, Georgia for a mean dose of 6.2 mg was $5270. However, the average cost of blood product transfusion ($4339) to the institution in this series was comparable ($193.76/U packed red blood cells, $39.14/U fresh-frozen plasma, $33.6/U cryoprecipitate, and $76.50/U platelets). The cost of returning to the operating room for reexploration should also be considered.

The major limitations of this study relate to its small sample size, retrospective nature, and lack of standardized treatment indications and dosing regimens. In addition, we did not compare patients treated with rFVIIa with a nontreated group. However, these patients were administered rFVIIa only as a last resort when fatal exsanguination appeared imminent. Reexploration was performed before its administration to exclude surgical sources of bleeding. The patients who did not undergo reexploration had profound microvascular coagulopathy that was observed at the end of the first operation or had coagulopathy that failed to correct despite the transfusion of blood products or other hemostatic agents (aprotinin or desmopressin). Under these conditions, rFVIIa administration appears to have been successful in promoting hemostasis, reducing transfusions, and preventing further reexploration.

Further systematic investigations will be necessary to determine the safety and efficacy of this agent in cardiovascular surgery patients with intractable postoperative hemorrhage. Prospective analyses will be necessary to define standardized treatment indications and dosing regimens before this agent can be broadly applied to bleeding adult cardiovascular surgical patients.

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