Safety and efficiency of recombinant activated factor VII in postcardiotomy massive hemorrhage

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Postoperative massive hemorrhage is a difficult clinical situation after cardiac surgery. Recombinant activated factor VII (rf-VIIa) can be a useful adjunct to surgical hemostasis and blood product transfusion. Four cases of massive hemorrhage treated with rf-VIIa after complex cardiac surgery are reported. A review of the literature and possible guidelines for the use of rf-VIIa in cardiac surgery are provided.

Key Words: Coagulation; Complications; Hemorrhage; Surgery

Postcardiotomy massive hemorrhage remains a difficult issue after complex cardiac surgery. Several strategies can be applied to control bleeding, including surgical intervention, local hemostatic agents and blood products. Recombinant activated factor VII (rf-VIIa) has been proposed as an efficient adjunct to standard hemostatic strategies in postcardiotomy patients with significant hemorrhage (1). A number of reports have described significant complication rates with rf-VIIa, thus questioning its safety (2-5).

Four patients with life-threatening hemorrhage were treated successfully with rf-VIIa at the Montreal Heart Institute (Montreal, Quebec) between December 2004 and November 2005. Patient medical history, surgery and outcomes are discussed followed by a review of the current literature.

Patient 1

The first patient was a 64-year-old man who had uncorrected tetralogy of Fallot and had undergone a previous Brock procedure (closed infundibular resection) with the placement of a Blalock-Taussig shunt; he was thus cyanotic. He also underwent anticoagulation for atrial fibrillation. The patient underwent ventricular septal defect and atrial septal defect closures, infundibuloplasty, pulmonary valve replacement, tricuspid valve repair and the Maze procedure. Immediately after surgery, the patient was coagulopathic and despite normalization of his coagulation factors, he continued to bleed, with a postoperative loss of 1.7 L over 6 h. He was explored, but no bleeding source was identified. Bleeding resumed a few hours later at a rate of 200 mL/h without coagulation abnormalities (Table 1); therefore, reintervention was necessary. Once again, no active bleeding site was identified and the bleeding resumed. The patient's platelet count, coagulation profile (Table 2), pH, calcium levels and temperature were carefully adjusted, and rf-VIIa 6 mg was administered. The bleeding stopped immediately and no other transfusion was required. He was extubated 36 h after surgery and left hospital after an uneventful stay.

La sécurité et l'efficacité du facteur VII activé recombinant dans l'hémorragie massive postcardiotomique

L'hémorragie massive postopératoire est une situation clinique difficile après une chirurgie cardiaque. Le facteur VII activé recombinant (rf-VIIa) peut être un ajout utile à l'hémostase chirurgicale et à la transfusion de produit sanguin. On rend compte de quatre cas d'hémorragie massive traités par rf-VIIa après une chirurgie cardiaque complexe. On fournit une analyse des publications scientifiques et des lignes directrices possibles sur l'utilisation du rf-VIIa en cas de chirurgie cardiaque.

Patient 2

The second patient was a 77-year-old woman with an aneurysmal ascending aorta and arch reaching 61 mm. She had an aortic replacement with an elephant trunk procedure (aortic arch replacement) with a 18°C, 35 min circulatory arrest and selective antegrade cerebral perfusion. After surgery, significant blood loss was experienced; she was taken back to operating room after 700 mL of chest tube drainage. Even though no surgical bleeding was identified, she had significant bleeding after the re-exploration and was taken back to operating room for a second reintervention after significant transfusions (Table 2). During her second reintervention, rf-VIIa 4.8 mg was administered, and the bleeding stopped in the minutes following administration; no adverse hemodynamic reaction was noted. She was not transfused after rf-VIIa administration. Hemiparesis was discovered the day following surgery without objective computed tomography scan deficit, and the patient recuperated totally during hospitalization. Two days after the surgery, a left superior lobe pneumonia was noted and she could be extubated only 17 days after surgery. She was discharged from hospital after a 30-day hospitalization.

Patient 3

A 21-year-old man suffered from cardiogenic shock with a regurgitant bicuspid aortic valve and an aneurysmal ascending aorta. His left ventricular ejection fraction was 10% and pulmonary artery pressure was 79/37 mmHg. A preoperative chest computed tomography scan showed acute lung injury. The operative procedure consisted of an emergent Bentall procedure, including a 9 min circulatory arrest at 25°C. Significant blood loss (1.8 L) followed the procedure, and the patient had a massive transfusion (Table 2). The patient was given rf-VIIa (4.8 mg intravenously) and stopped bleeding immediately; the chest was closed after 10 min. The patient was extubated on day 3 without requiring subsequent transfusion.

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TABLE 1
Coagulation profile

	Partial thromboplastin time (s)				International normalized ratio				Fibrinogen (units)			
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4
Preoperative	40.9	27	26.1	25	2.28	0.97	1.47	0.98	2.27	3.95	>12	3.8
Before rf-VIIa	38.5	107	48.1	50	1.05	1.15	0.09	1.48	3.5	2.08	5.95	3.8
After rf-VIIa	39	40.9	26.2	70	0.94	1.01	1.2	0.94	6.7	2.37	7.8	2.9

rf-VIIa Recombinant activated factor VII

TABLE 2
Drainage and blood products administration before recombinant activated factor VII (rf-VIIa) administration

	Drainage (mL)	Platelets (units)	Cryoprecipitates (units)	Packed red blood cells (units*)	Fresh frozen plasma (units)	rf-VIIa (µg/kg)
Patient 1	1700	20	16	15	22	100
Patient 2	2600	55	16	4	24	102
Patient 3	1800	12	8	3	8	76
Patient 4	800	12	16	7	8	84

*Blood retrieved and treated by a cell-saving device was not considered in the packed red blood cell count

TABLE 3
Oxygenation profile

	PaO ₂ (mmHg)				FiO ₂ (%)				PaO ₂ /FiO ₂ ratio			
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4
Preoperative	328	462	101	183	1	1	0.6	1	328	462	168	183
Before rf-VIIa	136	156	123	320	0.8	1	0.7	0.8	170	156	175	400
After rf-VIIa	94	151	182	147	0.8	1	0.5	0.4	117.5	151	364	368

FiO₂ Fraction of inspired oxygen; PaO₂ Partial pressure of oxygen; rf-VIIa Recombinant activated factor VII

Patient 4

This patient was a 41-year-old man with an ascending aortic aneurysm and severe aortic insufficiency who underwent an initial aortic valve-sparing root replacement (remodelling). The annulus was markedly dilated, and after plication, the aortic regurgitation was severe. The cardiopulmonary bypass (CPB) was re-established and aortic valve replacement was performed. After 4 h of CPB, the patient had significant coagulopathy and multiple blood product administration (Table 2). Finally, after 4.8 mg of rf-VIIa, bleeding was controlled, and the patient was transported to the surgical intensive care unit, where he was extubated 30 h following surgery. No transfusion was necessary after rf-VIIa administration.

The evolution of the coagulation profile, drainage and blood product administration, and oxygenation are shown in Tables 1, 2 and 3.

DISCUSSION

We report four patients who appeared to have benefited from rf-VIIa administration. All patients had previously received antifibrinolytics, as well as coagulation factor and platelet repletion; they did not need subsequent transfusion. One patient experienced transient hemiparesis after a complex arch surgery, which might have been related to rf-VIIa use. None of the patients had renal insufficiency or acute lung injury. Three of the four patients were extubated in less than three days, and all patients left the hospital and were in good functional status at the follow-up visit.

rf-VIIa was introduced to treat hemophilic (A or B) patients with active hemorrhage or as prophylaxis against bleeding in surgery for hemophilic patients.

The action of rf-VIIa is through a combination of tissue factors at the site of injury, and the activation of factors X to Xa and IX to

IXa. Xa then transforms prothrombin to thrombin, which converts fibrinogen to fibrin, exerting its local hemostatic role.

rf-VIIa was demonstrated as an effective means of reducing mortality, amount of bleeding and functional outcome after cerebral hemorrhage in a well-designed, placebo-controlled trial (6). Three randomized controlled trials (7-9) were published on surgical patients. rf-VIIa was associated with lower blood loss and transfusion rates in open prostatectomy (9). Only one prospective, placebo-controlled study (10), two case-control studies (11,12) and several case series (1,13-16) have been published that addressed the issue of rf-VIIa administration after cardiac surgery. The indication, doses, timing and cost issues are widely variable and are discussed in the present report.

In a small, prospective placebo-controlled trial, Diprose et al (10) prophylactically administered 90 µg/kg rf-VIIa or placebo to 20 patients after protamine administration in complex cardiac surgery. In an intent-to-treat analysis, there was no significant difference in terms of blood loss and transfusion requirement. However, when one patient was excluded from analysis because of protocol violation, patients in the rf-VIIa group required less transfusion and fewer blood products (13 units versus 105 units in the placebo group). Mortality and thromboembolism rates were not significantly different among groups. As the authors acknowledged, the small sample size and the protocol violation might have led to a type I error and misinterpretation of rf-VIIa efficacy in a prophylactic setting.

Karkouti et al (11) reported the largest series of cardiac surgical patients receiving rf-VIIa. In a propensity score-matched, case-control study, they compared 51 patients who received 2.4 mg to 4.8 mg of rf-VIIa with 51 matched patients and demonstrated an important reduction in hourly drainage after rf-VIIa administration.

TABLE 4
Summary of cardiac surgery literature

Authors (reference)	Study type	Population	Indication	Dose	Outcome
Diprose et al (10)	Randomized controlled trial (n=9)	Cardiac surgery (high-risk)	Prophylaxis	90 µg/kg	No difference in transfusion rate or blood loss
Karkouti et al (11)	Propensity-matched (n=51)	Cardiac surgery (high-risk)	Massive refractory blood loss	2.4 mg or 4.8 mg	Lower hourly drainage
Bishop et al (16)	Case series (n=12)	Cardiac surgery (high-risk)	Massive transfusion	100 µg/kg	Correction of coagulation profile and bleeding
Raivio et al (13)	Case series (n=16)	Cardiac surgery (high-risk)	Massive refractory blood loss	28 µg/kg–192 µg/kg (>200 mL/h)	Correction of bleeding in 13 of 16 patients
Al Douri et al (1)	Case series (n=5)	Cardiac valvular surgery	Massive refractory blood loss	30 µg/kg	Correction of bleeding
Romagnoli et al (12)	Case-matched (n=15)	Cardiac surgery	Intractable bleeding	1.2 mg	Less bleeding, transfusion and surgical re-exploration, and shorter ICU stay

ICU Intensive care unit

However, compared with controls, the postoperative recovery of patients in the rf-VIIa group was slower and required prolonged intubation; acute renal dysfunction and stroke were also more frequent. The indication for administration was massive refractory blood loss. Massive blood loss was defined as 2000 mL, transfusion of four units of packed red blood cells (PRBC) or drainage of more than 100 mL/h. Refractory bleeding was defined as the exclusion of a surgical source within 2 h of surgical exploration and reversal of heparin, or re-exploration in the operating room with antifibrinolytic administration and correction of the coagulation profile within 50% of the normal value. The dose was 4.8 mg for severe uncontrolled blood loss and 2.4 mg for less severe blood loss. Twenty of the 51 patients were re-explored before factor VIIa administration and 11 required re-exploration after rf-VIIa administration. In eight of the 51 patients (15%), the surgical bleeding site was identified after rf-VIIa administration. Among the seven patients receiving 4.8 mg of rf-VIIa, one patient had unmasked surgical bleed; 13 of the 44 patients receiving the 2.4 mg dose required a second dose to help identify the three surgical sources. When the rf-VIIa was administered in the operating room, a dryness of the surgical site was noticed in all patients, and the surgical source was more easily identified in the majority of patients presenting with residual bleeding. That study did not demonstrate a beneficial effect of rf-VIIa, but suggested a reduction in bleeding after administration of rf-VIIa in a liberal fashion without showing a cost-effectiveness analysis.

The case series by Bishop et al (16) describe 12 patients who received massive transfusions after complex cardiac surgery. These patients received rf-VIIa and did not require subsequent transfusion, and experienced a correction of the coagulation profile without complications.

Indication

Most authors suggest that massive and refractory bleeding should be present before rf-VIIa administration is considered. Aldouri et al (1) reported patients having massive bleeding – from 300 mL/h to 10,000 mL/h – before rf-VIIa administration, with subsequent substantial reduction in bleeding after administration in the operating room. Raivio et al (13) reported 200 mL/h as the cut-off for increased postoperative bleeding. In their 16 high-risk postoperative patients, hemostasis was obtained in 13 of 16 patients after VIIa administration. The other three patients developed multiple organ failure and died postoperatively. The available literature and guidelines suggest intensive efforts to correct coagulopathy with blood products before rf-VIIa administration. Antifibrinolytics, such as aprotinin and tranexamic acid, were used in most of the patients in case series and trials.

The use of rf-VIIa has been reported in extracorporeal membrane oxygenation (17-20) and left ventricular assist devices (21), but systemic and extracorporeal device thrombosis were observed (22). No randomized controlled trials are available to address the safety issue of rf-VIIa in extracorporeal support patients.

Dose (Table 4)

The recommended dose of rf-VIIa is 90 µg/kg in hemophilic patients (4). Smaller doses (20 µg/kg) were effective in surgical patients without blood dyscrasia (9-12). Cardiac surgical patients in various series have received doses ranging from 24 µg/kg to 192 µg/kg. With vials of 2.4 mg and 4.8 mg available, the dose may be calculated to avoid wastage (13) (4.8 mg = 70 µg/kg for a 70 kg patient).

Complications (Table 5)

One per cent to 10% of patients receiving rf-VIIa for hemophilia can suffer from arterial hypertension and coagulation disorders, namely, hemarthroses, bleeding and low fibrinogen levels. In fewer than 1% of cases, allergy to the drug, renal insufficiency, arterial hypotension and disseminated intravascular coagulation can occur.

Thrombosis is one of the main issues feared with the use of rf-VIIa in a cardiac surgical population; reports have suggested a variable proportion of thromboembolic complications – from 0% to 44%. Thrombosis was reported in 25% of cases in the series by Raivio et al (13). Nineteen per cent of their patients also had a complication that might have been caused by thromboembolism, namely, transient paraplegia and multiple organ failure, for a total of 44% of patients. Several case series (16-20) report no thromboembolic complications from rf-VIIa. Few series (14,15,23) address the safety of rf-VIIa in coronary artery bypass grafting surgery, with no adverse events reported. Reports suggest that the increased production of thrombin after rf-VIIa administration may lead to thrombus formation in patients with vulnerable atherosclerotic plaques (24) or a freshly damaged endothelial surface. Thrombosis of extracorporeal membrane oxygenation circuits was reported by several groups (3,22).

The largest series available from Karkouti et al (11) reported 29% acute renal failure, 4% liver failure, 8% stroke, 2% deep vein thrombosis or pulmonary embolism and 6% myocardial infarction in patients who received rf-VIIa.

Cost-effectiveness

rf-VIIa is an expensive adjunct to hemostasis. A single dose ranges from US\$2,000 to US\$15,330 per patient (2,14). Other blood

TABLE 5
Side effects of recombinant activated factor VII

Authors (reference)	Mortality (%)	Thromboembolism (%)	Renal failure (%)	Neurological complication (%)
Diprose et al (10)	0	22	0	11
Karkouti et al (11)	15	16	29	8
Bishop et al (16)	0	0	0	0
Raivio et al (13)	25	25–44	25	38
Al Douri et al (1)	20	0	0	0
Romagnoli et al (12)	0	13	7	13

products are used in bleeding cardiac surgical patients. The unit prices of PRBC, fresh frozen plasma (FFP), cryoprecipitates and platelets range from US\$300, US\$125 to US\$150, US\$20 and US\$60 to US\$70, respectively. Furthermore, aprotinin may be used in the majority of patients with complex pathologies that are prone to bleeding, with a mean cost of US\$1,000 to US\$1,500 per dose. In an editorial commenting on a 16-patient case series (13), Despotis et al (2) suggest that rf-VIIa may be cost-effective in high-risk patients, considering that aprotinin is covered by the Food and Drug Administration, because it is effective in reducing blood loss, transfusion and re-exploration by 50% to 90%. None of the reported series have formally studied cost-effectiveness; this issue remains to be explored.

Guidelines for rf-VIIa use

Consensus recommendations for the off-label use of rf-VIIa were recently published (25). These recommendations suggest that rf-VIIa should be appropriate in patients who have received significant clotting factor replacement, including more than six units of FFP, 12 units of platelets (if less than $50 \times 10^9/L$) and 10 units of cryoprecipitates (if the fibrinogen level is low in persisting significant hemorrhage).

Gowers et al (14) report that their guidelines for rf-VIIa use failed to control blood loss after massive transfusion (10 units of PRBC, 10 units of FFP, 10 units of platelets and 10 units of cryoprecipitates) and coagulopathy continued, despite a surgical and embolization procedure after a hematology consultation. Karkouti et al (11) suggested rf-VIIa administration in patients who have massive and refractory blood loss. Massive blood loss was defined as blood loss: in excess of 2000 mL; requiring transfusion of four units of PRBC; brisk enough to preclude sternal closure; or that exceeding 100 mL/h in an intensive care unit. Refractory blood loss was defined as: significant blood loss after exclusion of a surgical source by more than 2 h of surgical exploration after CPB;

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TABLE 6
Recommendations for recombinant activated factor VII (rf-VIIa) administration

Before rf-VIIa administration	Optimize systemic temperature Optimize ionized calcium levels Correct pH Correct platelet levels Correct international normalized ratio, prothrombin time and fibrinogen within 50% of normal Correct surgical bleeding sites
Administration	Dose: 40 µg/kg to 90 µg/kg
After rf-VIIa administration	Monitor oxygenation Monitor renal function Monitor and treat thromboembolic events

surgical re-exploration; or that which required administration of antifibrinolytics, five units of platelets and four units of FFP, with prothrombin time, international normalized ratio and platelet count within 50% of normal values and hematocrit greater than 24%. All patients were submitted for evaluation by a hematologist. Other investigators also suggested aggressive repletion of blood coagulation factors before administration of rf-VIIa (1,13). From all the available series, the concept of massive and uncontrollable blood loss appears to be the first prerequisite for the multidisciplinary decision of rf-VIIa administration. Table 6 suggests an algorithm for rf-VIIa administration.

CONCLUSIONS

We have reported four patients with complex cardiac surgeries that were followed by massive and uncontrollable bleeding who were repleted in coagulation factors and PRBC. All patients stopped bleeding and did not require any further transfusion of blood components after administration of rf-VIIa. One patient had a transient neurological event possibly related to rf-VIIa. No patients suffered from renal or pulmonary failure. We suggest the administration of 40 µg/kg to 90 µg/kg of rf-VIIa for patients who have massive non-surgical bleed in the operating room after consultation with anesthesiology and hematology departments, and after correction of the coagulation profile, pH and platelet count. We suspect that the administration of off-label rf-VIIa in the operating room could help to identify a persistent surgical bleeding source or respond to eventual thrombotic complications at the surgical site. Further randomized controlled studies are mandatory to regulate the use of this potent but potentially harmful drug, as was emphasized in a recent review article on off-label use of new biologics (26).

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