

Small-Dose Recombinant Activated Factor VII (NovoSeven®) in Cardiac Surgery

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Recombinant activated factor VII (rFVIIa) has been used at different doses in cardiac surgery patients. We tested the efficacy of small-dose rFVIIa in patients with intractable bleeding after cardiac surgery. The study group comprised 15 cardiac surgery patients with intractable bleeding treated with small-dose (1.2 mg) rFVIIa as a slow IV bolus at the end of complete step-by-step transfusion protocol. Fifteen matched patients undergoing the same transfusion protocol in the pre-rFVIIa era represented the control group. Blood loss at the end of the transfusion protocol was a primary outcome. Median, 25th–75th 24-h blood loss percentiles were 1685 (1590–1770) mL versus 3170 (2700–3850) mL in study group and controls, respectively ($P = 0.0004$). Transfused red blood cells, fresh-frozen plasma, and platelets in the study group and

controls were as follows: 7 (4–8) U versus 18 (12–21) U ($P = 0.001$); 7.5 (6–11) U versus 11 (9–15) U ($P = 0.003$); 0 (0–4) U versus 9 (6–13) U ($P = 0.001$). In addition, significant improvements of prothrombin time ($P = 0.015$), international normalized ratio ($P = 0.006$), activated partial prothrombin time ($P = 0.01$), and platelet count ($P = 0.003$) were detected in the study group versus controls. Finally, patients receiving rFVIIa showed a reduced intensive care unit length of stay ($\chi^2 = 15.9$, $P = 0.0001$) and had infrequent surgical re-exploration ($\chi^2 = 16.2$, $P < 0.0001$). Small-dose rFVIIa showed satisfactory results in cardiac patients with intractable bleeding. Further randomized studies are necessary to confirm our findings.

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Hemorrhagic complications after cardiac surgery are an important cause of death and resource utilization (1). Factors contributing to blood loss and transfusion after cardiac operations include cardiopulmonary bypass (CPB), hemodilution, platelet (PLT) consumption-dysfunction, consumption of clotting factors, deep hypothermia, inflammatory cascade activation, and fibrinolysis (1).

Multiple approaches to decrease blood loss in this population have been proposed, with varying degrees of success (1,2). In recent years, there has been an increased use of recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) for the treatment of refractory bleeding in several patient populations (3), and, more recently, it has been used at different doses in cardiac surgery (4–7).

The present study tested the efficacy of small-dose rFVIIa in patients with intractable bleeding after cardiac surgery.

Methods

Significant bleeding was considered as bleeding that compromised hemodynamics and/or ≥ 500 mL/h during the first postoperative hour or ≥ 300 mL/h for 3 consecutive hours after chest closure, or ≥ 1200 after the fifth postoperative hour (8). Red blood cells (RBC_s) were given to maintain the hemoglobin concentration at least 7 g/dL during CPB and 9 g/dL during the postoperative period. According to our institutional guidelines, subjects with significant bleeding underwent the following step-by-step transfusion protocol: if prothrombin time (PT) exceeded 1.5 times the control values, 10–15 mL/kg of fresh-frozen plasma (FFP) was administered (9). If critical bleeding persisted, one unit of pooled PLT concentrates/10 kg body weight was transfused followed by 1000 IU of prothrombin complex concentrates (PCC) (10).

Blood loss was considered intractable when all the following criteria were met:

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Table 1. Preoperative Variables

	Study (n = 15)	Controls (n = 15)	P
Age (yr)	66.3 ± 12.7	75.3 ± 8.6	ns
Female	13 (86.6)	12 (80)	ns
BSA	1.7 ± 0.1	1.8 ± 0.2	ns
Diabetes	2 (13.3)	3 (20.0)	ns
Hypertension	3 (20.0)	3 (20.0)	ns
Hyperlipidemia	1 (6.60)	1 (6.60)	ns
AF	2 (13.3)	3 (20.0)	ns
NYHA	3 (3-4)	3 (3-3.5)	ns
CCS	2 (1-3)	2 (1-3)	ns
Euroscore			
Additive	8.0 (5-9)	8.2 (5-8)	ns
Logistic	14.0 (11-18)	15.2 (10-18)	
CHF	2 (13.3)	3 (20.0)	ns
Left ventricular dysfunction	2 (13.3)	3 (20.0)	ns
MI	1 (6.60)	1 (6.60)	ns
Renal insufficiency	1 (6.60)	1 (6.60)	ns
CVA	2 (13.3)	3 (20.0)	ns
COPD	3 (20.0)	2 (13.3)	ns
PVD	1 (6.60)	1 (6.60)	ns
Surgical indications			
CAD	2 (13.3)	3 (20.0)	
Valve Disease	2 (13.3)	2 (13.3)	
CAD+ Valve disease	2 (13.3)	5 (33.3)	ns
TAAD	4 (26.6)	2 (13.3)	
Others	5 (33.3)	3 (20.0)	
Antiplatelet therapy	4 (26.9)	5 (33.3)	ns
Anticoagulant therapy	2 (13.3)	2 (13.3)	ns

Continuous variables are presented as mean ± 1 SD; discrete variables are presented as percentages (in parentheses). Nonparametric data are shown as median (25th-75th percentile). Left ventricular dysfunction is defined as ejection fraction ≤35%. Renal insufficiency is defined as a creatinine level >2 mg/dL.

ns = not significant; BSA = body surface area (kg/m²); AF = atrial fibrillation; NYHA = New York Heart Association functional class; CCS = Canadian Cardiovascular Society functional class; CHF = (signs/symptoms of) congestive heart failure; MI = myocardial infarction; CVA = cerebrovascular accident; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CAD = coronary artery disease; TAAD = type A acute aortic dissection.

A surgical bleeding source was excluded by an accurate surgical exploration at the end of CPB and reversal of protamine and/or a surgical bleeding source was excluded at surgical re-exploration.

Patients received antifibrinolytics (10 mg/kg bolus of tranexamic acid followed by an infusion of 1 mg · kg⁻¹ · h⁻¹ for the duration of the procedure and, in case of re-intervention or acute aortic dissection, 2,000,000 KIU aprotinin before CPB followed by 2,000,000 KIU in CPB-prime and 500,000 KIU/h for the duration of the procedure).

Patients completed the transfusion protocol (administration of RBCs PLT, FFP, and PCC).

Coagulation measures (PT, partial thromboplastin time, International Normalized Ratio [INR], and fibrinogen [FBG]) and PLT count were corrected within 50% of normal value.

From January 2004 to January 2005 1212 consecutive patients underwent cardiac surgery at our institution (Cardiac Surgery, Careggi Hospital, Florence, IT). Among them, 76 (6.3%) suffered from intractable bleeding. All patients with intractable bleeding underwent the step-by-step transfusional protocol following the above-mentioned institutional guidelines for transfusion therapy. Starting from October 2005, 15

consecutive unselected intractable bleeding patients with persistent blood loss after conventional transfusion therapy were treated with small-dose rFVIIa and they were the study group. All records of the remaining intractable bleeding patients receiving only conventional transfusion protocol between January 2004 and September 2005 in the pre-rFVIIa era, were reviewed and 15 controls were identified matching patients 1:1 to the study population for perioperative characteristics. Units of RBCs, PLT, FFP, and PCC at the end of the transfusion protocol were comparable for treated patients and controls (not significant).

In case of intractable bleeding after completion of a standard infusion protocol, patients underwent surgical re-exploration and/or RBCs, PLT, and FFP transfusion. Preoperative data are displayed in Table 1.

Starting from September 2005 rFVIIa was used as rescue therapy for patients with intractable bleeding at our institution. The therapy consisted of small-dose (1.2 mg) rFVIIa given as a slow IV bolus. This dose was chosen empirically after examination of published reports. Doses ranged from 11.1 μg/kg to 21.5 μg/kg (median, 17 μg/kg; 25th-75th percentiles, 15-18.4 μg/kg). The infusion was repeated in case of persistent bleeding (>100 mL/h). If blood loss exceeded 100

mL/h or re-exploration was necessary, the treatment with rFVIIa was considered unsuccessful.

Blood loss was judged by attending surgeons and anesthesiologists who made the final decision about the appropriateness of the use of rFVIIa for each patient. The screening for thromboembolic events was made by physical examination. If a thromboembolic complication was suspected, color Doppler sonography, transesophageal echocardiography, computed tomography scan and laboratory tests were performed to confirm the diagnosis.

Study end-points were considered at the end of the standard step-by-step transfusion protocol. Blood loss was the primary outcome explored either as hourly bleeding or as 1-3-5-24-h bleeding. The need for RBCs, FFP, and PLT transfusion in study patients after the administration of rFVIIa was compared with controls.

Laboratory evaluation included PT, INR, activated prothrombin time (aPTT), FBG, and PLT count.

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects (11), approval was deemed to be unnecessary by the institutional ethics board. Furthermore, as rFVIIa was mainly used as rescue therapy in critically ill patients and there were no experimental interventions, they judged the informed consent not applicable. However, ethics board approval was obtained to review records of patients receiving rFVIIa as well as the records of all patients undergoing cardiac surgery between 2004 and 2005 to identify controls.

All patients were premedicated with morphine hydrochloride 0.1 mg/kg and scopolamine 40 µg/kg IM 30 min before transport to the operating room.

The induction of the anesthesia was achieved with sufentanil 1 µg/kg and midazolam 0.1 mg/Kg and maintained with sufentanil 1 µg · kg⁻¹ · h⁻¹ and propofol 3 mg · kg⁻¹ · h⁻¹. Muscle relaxation was achieved with cisatracurium 100 µg/kg. After intubation of the trachea, the lungs were ventilated with 50% oxygen in air using a semi-open circle system. Tidal volume and ventilatory rate were adjusted to keep the arterial carbon dioxide partial pressure between 35 and 40 mm Hg.

Before the initiation of CPB, patients received porcine heparin at an initial dose of 300 U/kg, injected IV before cannulation of the aorta. An additional dose of 5000 U of heparin was administered when the kaolin activated clotting time (ACT) was <400 s (12). Anticoagulation for off-pump coronary artery bypass grafting was obtained with heparin at a dose of 150 U/kg to achieve an ACT target of 300 s (13). An additional dose of 2500 U was given if the ACT declined below 300 s (2). After complete weaning from CPB, or the end of the off-pump coronary artery bypass grafting, heparin was neutralized by IV infusion of protamine hydrochloride at the dose of 0.6 mg per

Table 2. Operative Data

	Study (n = 15)	Controls (n = 15)	P
Emergency	4 (26.6)	3 (20.0)	ns
Redo surgery	3 (20.0)	2 (13.3)	ns
Procedures			
Isolated CABG	2 (13.3)	2 (13.3)	
OPCAB	2 (13.3)	2 (13.3)	
Isolated VP	3 (20.0)	2 (13.3)	ns
CABG + VP	2 (13.3)	4 (26.6)	
AAR	6 (40.0)	5 (33.3)	
CPB time	135 (85-185)	172 (110-248)	ns
CCL time	76 (66-120)	105 (75-136)	ns
DHCA	4 (26.6)	4 (26.6)	ns
DHCA time	35 (16-36)	36 (19-89)	ns
ACP	3 (20.0)	3 (20.0)	ns
ACP time	18 (11-49)	12 (36-57)	ns

Continuous variables are presented as mean ± 1 SD; discrete variables are presented as percentages (in parentheses). Nonparametric data are shown as median (25th-75th percentile).

ns = not significant; CABG = coronary artery bypass grafting; OPCABG = off-pump coronary artery bypass grafting; VP = Valve procedures; AAR = ascending aorta replacement; CPB = cardiopulmonary bypass; CCL = cross-clamp; DHCA = deep hypothermic circulatory arrest; ACP = antegrade cerebral perfusion.

100 U of heparin administered (12). Heparin neutralization was considered adequate if post-protamine ACT value was within 10% of the pre-heparin value.

Patients in the two groups were operated on by three surgeons. The intensive care unit (ICU) staff (physicians) was the same and anesthetic management was identical in the two groups. Surgery was performed through a median sternotomy on CPB with antegrade/retrograde cold blood cardioplegia. The lowest temperature achieved was 34°C (21°C in patients who underwent deep hypothermic circulatory arrest). Operative data are displayed in Table 2.

All data were analyzed with the SPSS for Windows, release 11.0 (SPSS Inc., Chicago, IL). Continuous data are presented as mean ± SD; discrete variables are given as percentages. Non-normally distributed variables are presented as median and interquartile range. Continuous variables were compared by Student's paired and unpaired Student's *t*-tests or analysis of variance, where appropriate. Tukey's test was used for *post hoc* comparisons. Two-way analysis of variance was used to assess whether any difference occurred in postoperative bleeding as well as in laboratory findings between patients receiving tranexamic acid versus aprotinin.

Percentages were compared by χ^2 contingency analysis. Mann-Whitney tests were used for unpaired nonparametric data. Based on 24-h blood loss at the end of the transfusion protocol as a primary outcome, this study had 80% power to detect a 50% difference in 24-h bleeding. A two-tailed *P* value of less than <0.05 adjusted for multiple comparisons was judged to be statistically significant.

Table 3. Coagulation Laboratory Findings

	Study				Control Group			
	Baseline	TP	24 h	<i>P</i> *	Baseline	TP	24 h	<i>P</i>
PT	86.0 ± 21.9	63.3 ± 18.7	92.9 ± 30.4‡§	0.024	87.4 ± 15.1	50.3 ± 20.7†	66.7 ± 12.8‡	<0.0001
INR	1.3 ± 0.7	1.5 ± 0.3	1.0 ± 0.2‡§	0.03	1.1 ± 0.2	1.9 ± 0.9	1.3 ± 0.1	0.009
APTT	32.3 ± 1.9	60.8 ± 23.4†	41.1 ± 16.9‡	0.002	46.9 ± 25.7	88.1 ± 64.3†	46.2 ± 12.2‡	0.033
FBG	375.3 ± 121.7	212.5 ± 68.5†	260.0 ± 77.9‡	0.001	396.3 ± 122.7	256.5 ± 147.9†	317.3 ± 130.1‡	ns
PLT	191.2 ± 73.8	92.6 ± 42.1†	106.9 ± 51.4‡§	0.001	189.1 ± 56.1	89.9 ± 59.8†	62.9 ± 38.5‡	<0.0001

Variables are presented as mean ± sd. *Significance at repeated measures analysis of variance. †‡Significance versus baseline and end of transfusion protocol, respectively. §Significance at unpaired Student's *t*-test.

ns = not significant; TP = (End of) trasfusalional protocol; 24 h = 24 h from the end of the trasfusalional protocol; PT = prothrombin time (%); INR = international normalized ratio; APTT = activated prothrombin time (s); FBG = fibrinogen (mg/dL); PLT = platelet count ($n \times 10^9/L$).

Results

Three patients died in the control group (20%). The causes of death were a low-output syndrome (on postoperative day 2), multiorgan failure (on postoperative day 3), and respiratory failure (on postoperative day 15). In contrast, no death occurred in the Study Group ($\chi^2 = 1.5$, not significant). In comparison to controls, patients receiving rFVIIa had significantly more complications (33.3%, $n = 5$ versus 20%, $n = 3$; $P = 0.006$). Complications were as follows: stroke in 2 patients (study group), renal failure in 2 (1 study group, 1 control), 1 respiratory failure (study group), low-output syndrome (1 study group, 1 control), infection (1 control group). Patients in the study group had a shorter ICU length of stay (LoS) (142 h, 25th–75th percentiles, 93–176 h versus 427 h, 388–576 h; $P = 0.0008$). In addition, 40% of study patients had a LoS >48 h versus 100% in the control group ($\chi^2 = 15.9$, $P = 0.0001$).

Thirteen patients in the control group (86.6%) underwent surgical re-exploration and, during surgery, we did not find a specific surgical bleeding source. In contrast, no patient receiving rFVIIa required surgical re-exploration ($\chi^2 = 16.2$, $P < 0.0001$). Twenty-four hour blood loss after the end of the transfusion protocol was 1685 (1590–1770) mL and 3170 (2700–3850) mL in the study group and controls, respectively ($P = 0.0004$). In patients receiving rFVIIa hourly bleeding reduced from 490 (340–750) mL to 70 mL (38–90) mL; $P < 0.001$). In controls hourly bleeding was 348 (250–535) mL. In this group blood loss was not significantly reduced at 1 h (285 [35–320] mL; not significant), 3 h (298 [188–342] mL; not significant), or 5 h (230 [159–310] mL; not significant) from the end of the transfusion protocol, respectively. There was no statistical significance for blood loss in patients receiving aprotinin versus those receiving tranexamic acid ($P = 0.932$). There was a statistically significant reduction in transfusion requirements for RBCs (7 [4–8] U versus 18 [12–21] U; $P = 0.001$), FFP (7.5 [6–11] U versus 11 [9–15] U; $P = 0.003$) and PLT (0 [0–4] U versus 9 [6–13] U; $P = 0.001$) in study patients and controls, respectively.

Results are shown in Table 3. PT varied significantly over time in the 2 groups ($P = 0.024$ and $P < 0.0001$ in study patients and controls, respectively). Nonetheless 24 h after the end of the transfusion protocol, PT (%) was increased in patients who received rFVIIa ($P = 0.015$). Accordingly, INR showed a significant reduction in the 2 groups ($P = 0.03$ and $P = 0.009$ in study patients and controls, respectively). Nevertheless, compared with the end-transfusion protocol value, INR after 24 h was significantly reduced in the study group ($P = 0.003$). Furthermore, aPTT showed a significant improvement in treated patients ($P = 0.002$) and controls ($P = 0.033$); however, the 24-h end-transfusion protocol values were not significantly different. FBG changed over time in the study group ($P = 0.001$) whereas it did not vary in controls at different observational times. However, 24-h end-transfusional protocol FBG did not differ between groups (not significant). Finally, in both groups, PLT count was significantly reduced ($P = 0.001$ and $P < 0.0001$, respectively). However, the 24-h value was significantly increased in the study group ($P = 0.034$). No significant difference was detected between patients receiving tranexamic acid compared with those receiving aprotinin (not significant).

Discussion

There is excessive bleeding during the first 24 postoperative hours in 5%–7% of patients undergoing cardiac surgery, and a surgical bleeding site can be detected in less than half of the re-explored patients (11). Multiple approaches to decrease blood loss in cardiac surgery patients have been tested with different results (1,2). In recent years, rFVIIa has been used in cardiac surgery patients with intractable bleeding. In these patients satisfactory coagulation was obtained with doses ranging from 15 to 180 $\mu\text{g}/\text{kg}$, and repeated injections were sometimes necessary as a result of the rFVIIa short plasma elimination half-life (Table 4) (5–7,12,14–29).

In this report a small-dose regimen of rFVIIa was tested. A dose of 1.2 mg, the smallest dose available in

Table 4. rFVIIa in Adult Cardiac Surgery

Author(s)	Year	Patients	Study	Dose	No. of doses*
Al Douri M (15)	2000	4	Open pilot study	30 μ g/kg	Single
Hendriks HGD (5)	2001	1	Case report	90 μ g/kg	Single
Von Heymann (6)	2002	1	Case report	50 μ g/kg	2
Kastrup M (16)	2002	1	Case report	40 μ g/kg	Single
Potapov V (17)	2002	1	Case report	120 μ g/kg	2 (60)
Diprose P (18)	2002	7	Retrospective observational	22 μ g/kg	Single
Ziętkiewicz M (19)	2002	1	Case report	20 μ g/kg	2 (30)
O'Connell NM (20)	2003	5	Retrospective observational	15-180 μ g/kg	n
Stratmann G (21)	2003	1	Case report	90 μ g/kg	2
Eikelboom JW (22)	2003	5	Case series	100 μ g/kg	?
Naik VN (23)	2003	1	Case report	107 μ g/kg	1
Tanaka KA (7)	2003	2	Case series	45 μ g/kg	2 (60)
Herbertson M (24)	2004	17	?	13-90 μ g/kg	?
Vanek T (25)	2004	7	Retrospective observational	90 μ g/kg	2 (40)†
Gill R (26)	2004	15	Retrospective observational	24 μ g/kg	1
Flynn JD (27)	2004	1	Case report	90 μ g/kg	1
McIlroy (DP) (4)	2004	1	Case report	90 μ g/kg	1
Aggarwal A (28)	2004	24	Retrospective observational	90 μ g/kg	n
Kogan A (29)	2004	1	Case report	-	-
Karkouti K (30)	2005	51	Matched case control	62.37 μ g/kg	2 (62)‡§, 2 (37)§

* Doses of further administrations are reported between parentheses. † In 2 patients; ‡ In 1 patient; § n 13 patients ? n = not reported.

United States, which is economically very attractive. The question is whether this dose is effective and safe.

To test this hypothesis, 15 patients who received small-dose rFVIIa were evaluated and compared to 15 case-matched patients. The control group tended to be older and had longer bypass and cross-clamp times, although these differences did not reach statistical significance.

In our experience, small-dose-rFVIIa significantly reduced postoperative bleeding. Furthermore, treated patients needed less RBCs, FFP, and PLT transfusion, and they had a reduced re-exploration rate, ICU LoS and mortality. Furthermore, 24 hours after the end of the transfusion protocol, PT (%) was increased in patients who received rFVIIa ($P = 0.015$), and, accordingly, INR was significantly reduced in the study group ($P = 0.003$). Finally, PLT count was significantly higher in patients treated with rFVIIa ($P = 0.034$), whereas aPTT and FBG did not differ between groups (not significant). The use of aprotinin or tranexamic acid did not significantly influence results.

In a recent report, Karkouti et al. (30) examined 51 cardiac surgery patients with intractable blood loss who received a dose of rFVIIa ranging from 2.4 to 4.8 mg. In comparison with their matched controls, these patients showed decreased blood loss and a reduced use of blood products. Nevertheless, treated patients had a significant ICU and hospital LoS as well as an increased incidence of acute renal dysfunction compared with the matched control patients. The strength of this study is the accurateness of patient selection/matching by propensity analysis. Nevertheless, control patients were not comparable to the study population for number units of RBCs, PLTs, plasma, and

cryoprecipitate transfused ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P = 0.0004$, respectively), and this, in our opinion, increases the bias in the assessment of the effectiveness of rFVIIa. In the present study, patients and controls received comparable units of RBCs, FFP, PLTs, and PCC; thus our patient population was more homogeneous and this allowed a more accurate analysis of rFVIIa's effects.

The safety of combined administration of rFVIIa and other procoagulant factors is still a debated issue. Key et al. (31) showed a synergic procoagulant effect between PCC and rFVIIa, and Bui et al. (32) reported a fatal thrombosis after administration of activated complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received rFVIIa. In our opinion, this complication could not be related to the association rFVIIa/PCC, as PCC was given 6 hours after rFVIIa, an interval longer than the rFVIIa half-life time (2-3 hours). Moreover, unlike us, those authors used larger doses (90 μ g/kg) of rFVIIa, whereas the dose of PCC was unspecified.

Cardiac surgery patients and those affected by coronary artery disease represent high-risk categories for systemic or localized thrombosis after rFVIIa, as recently suggested by Goodnough et al. (3). Nevertheless, despite use of rFVIIa in more than 150 cardiac surgery patients during the last 5 years, the incidence of this serious adverse event remains very small. This can be theoretically explained by the presence of some protective mechanisms such as the large plasma concentration during CPB of tissue factor pathway inhibitor, a strong inhibitor of the enzymatic activity of the TF-FVIIa complex (18,33). However, even though published data showed a good level of safety in cardiac

surgery patients, these subjects must be considered at high risk for thrombotic complications and, when treated with rFVIIa, they must be carefully monitored. Particularly, the influence of rFVIIa on graft patency after coronary artery bypass grafting (CABG) is still unknown, and many authors believe the use of rFVIIa to be contraindicated in these subjects (3). Among our 15 treated patients, 2 underwent CABG and they showed no clinical, electrocardiographic, or echocardiographic signs of graft occlusion. Two study patients had postoperative stroke; in both a predisposing factor for cerebrovascular accident was clearly identified: the first patient had preoperative transient ischemic attacks followed by stroke occurring 8 months before surgery, resulting in complete functional recovery. The second underwent prolonged deep hypothermic circulatory arrest with postoperative hypoperfusion resulting in multiple ischemic injuries shown by postoperative computed tomography. In the remaining patients, the use of rFVIIa caused no thromboembolic complications as assessed by clinical examination, laboratory tests, and transesophageal echocardiography.

Besides conventional laboratory tests, thromboelastography has been demonstrated to provide a more accurate evaluation of the overall clotting process (34). Hendriks et al. (35) demonstrated that rFVIIa not only influences the speed of clot formation but also the physical properties of the clot not detectable by routine coagulation tests. Indeed, in their study r (initiation of fibrin formation) and k and α angle (speed of clot formation) significantly improved after administration of rFVIIa.

Our investigation presents some limitations, which need to be considered. This study was not randomized and prospective. The small number of patients reduced the strength of statistical analysis. Because of the small number of patients in each group receiving the same rFVIIa dose, we were unable to perform patient analysis according to the dosage of NovoSeven used. The number of patients undergoing CABG was quite small. In addition no subject was quantitatively evaluated with coronary angiography postoperatively. Thus, we failed to achieve definite conclusion about the safety of rFVIIa on graft patency. We tested the effect of rFVIIa given after a complete transfusion protocol. The effect of rFVIIa without a previous administration of other coagulation factors should be tested to explore if rFVIIa's coagulation effect is mainly attributable to its interaction with other factors such as PCC. Laboratory monitoring of the efficacy of rFVIIa was mainly based on PT, INR, aPTT, FBG, thromboelastography, and the endogenous thrombin potential measured in PLT-rich plasma would have been more helpful.

Nonetheless a strength of our study, in our opinion, is that it included patients treated at a single institution according to standardized clinical guidelines. The patient population was homogeneous and this allowed us to assess the effectiveness of rFVIIa with a greater accuracy than previous studies.

Even with the above-mentioned limitations we can conclude that, in our experience, small-dose rFVIIa can be considered effective for intractable bleeding after cardiac surgery. Further larger randomized trials will better provide evidence of the effective value of rFVIIa in this setting.

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