

Recombinant activated factor VII for uncontrolled bleeding postcardiac surgery



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A retrospective observational study to review the safety and efficacy of rFVIIa in persistent hemorrhage in post cardiac surgical patients.

Methods: Patients who had bleeding of 3 ml/kg/h or more for 2 consecutive hours after cardiac surgery were arranged into two groups; control group, who received conventional treatment and rFVIIa group, who received conventional treatment and rFVIIa.

Results: There was no significant difference in demographic and surgical characteristics of both groups. The chest tube output significantly decreased in the rFVIIa group compared to the other group 4 hours after admission {1.4 (IQR: 1–2.2) ml/kg/h vs 3.9 (IQR: 3.1–5.6) ml/kg/h; $p = 0.004$ } and continues to be significant till 9 hours after CSICU admission {0.6 (IQR: 0.4–1.1) ml/kg/h vs 1.9 (IQR: 1.2–2.2) ml/kg/h; $p = 0.04$ }. The median number of blood products units transfused to rFVIIa group was significantly lower compared to control group in the period from 3–12 hours after CSICU admission. 13 (5.5%) patients in rFVIIa group had Thromboembolic adverse events (TAE) compared to 7 (2.4%) patients in other group $p = 0.27$. 8 patients in the rFVIIa group needed reexploration compared to 19 patients in the other group, $p = 0.01$. No significant difference was noticed between the 2 groups regarding: new onset renal failure, median number of mechanical ventilator days, pneumonia, mediastinitis, ICU and hospital lengths of stay, survival at 30 days and at discharge.

Conclusion: In this analysis, rFVIIa successfully reduced the chest tube bleeding and blood products transfused during severe post cardiac surgical bleeding. However, safety of rFVIIa remains unclear. Prospective controlled trials are still needed to confirm the role of rFVIIa.

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Introduction

Despite improvements in surgical skills and strategies, bleeding remains a problem in cardiac surgery. Bleeding is also a significant cause of morbidity and mortality, prolonged hospital stay, and increased cost [1,2]. Increased risk of postoperative complications as well as reduced short- and long-term survival is associated with the transfusion of red cells that have been stored for >2 weeks in patients undergoing cardiac surgery [3]. Other reports argue that for patients undergoing cardiac surgery, bleeding contributes to mortality through mechanisms unrelated to blood transfusion [4]. Efforts to minimize the use of limited resources such as blood products are essential and the most obvious and probably the most effective strategy is to improve surgical techniques and hemostatic management.

Recombinant activated factor VII (rFVIIa) is a potent prohemostatic agent currently approved for bleeding in patients with hemophilia or other congenital hemostasis and coagulation defects. Over the past years, the estimated number of patients treated with rFVIIa has grown rapidly, mainly for off-label indications, including excessive bleeding after trauma and cardiac operations [5–10].

The rFVIIa promotes hemostasis by enhancing the generation of thrombin on platelets. rFVII complexes with all available tissue factor to activate factor X directly and induce thrombin generation. This results in the formation of a tight and stable fibrin plug that is resistant to premature fibrinolysis [11].

The aim of our work is to present our experience of the use of rFVIIa in treating intractable hemorrhage postcardiac surgery in adult patients with respect to its efficacy and safety.

Materials and methods

The study was conducted in the Cardiac Surgical Intensive Care Unit (CSICU), King Faisal Heart Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

Patients

Retrospectively, the medical charts of all adult patients ($n = 4856$) who had cardiac surgery in the period between February 2004 and December 2013 were screened for the occurrence of postoperative bleeding in the intensive care unit (ICU). Patients who were younger than 18 years, those

Abbreviations

rFVIIa	recombinant activated factor VII
CSICU	Cardiac Surgical Intensive Care Unit
TAE	Thromboembolic Adverse Events
CVA	Cerebrovascular accidents
MI	Myocardial infarction
PE	Pulmonary embolism
DVT	Deep venous thrombosis
ml/kg/h	milliliter/ kilogram/hour
IQR	Interquartile range
aPTT	activate partial thromboplastin time
ACT	activated Clotting time
INR	international normalized ratio
gm/l	gram/Liter
mcg/kg	microgram/ kilogram
CPB	cardiopulmonary bypass
FFP	fresh frozen plasma
Cryo	cryoprecipitate
ICU	intensive care unit
35.5 C	35.5 degree celsius
mg/dl	milligram/deciliter
RBCs	red blood corpuscles
TAFI	thrombin activation fibrinolysis inhibitor
PT	pro-thrombin time
RCT	Randomized Controlled Studies
FEIBA	Factor Eight Inhibitor Bypass Activity

who had a primary coagulation defect, pregnant women, those who received rFVIIa in the operating room, those having surgery for the correction of congenital heart diseases, requiring a mechanical circulatory support device, or extracorporeal membrane oxygenation in the operating room were excluded ($n = 42$). All patients who had chest tube bleeding of ≥ 3 mL/kg/h for ≥ 2 consecutive hours postadmission to CSICU from the operating room ($n = 441$) were included in the study and arranged in two groups: control group [those who received conventional treatment; Fig. 1 boxes 2, 4, and 6 ($n = 207$)]; and the rFVIIa group [those who received conventional treatment and rFVIIa; Fig. 1 boxes 2, 4, 6, and 7 ($n = 234$)].

The study protocol was approved by King Faisal Research Center and Medical ethics committee. Being a retrospective chart review study, consent was waived by the ethical committee.

The patients' demographics, preoperative comorbidities, preoperative anticoagulation, priority of surgery, type of surgery, cardiopulmonary bypass time (CPB), aortic cross clamp time, and surgical re-exploration were collected. The European System for Cardiac Operative Risk Evaluation II score system was used to assess the severity for each patient [12].

Coagulation parameters (international normalized ratio, activated partial thromboplastin time, activated clotting time, and fibrinogen levels) and platelets count were measured on admission

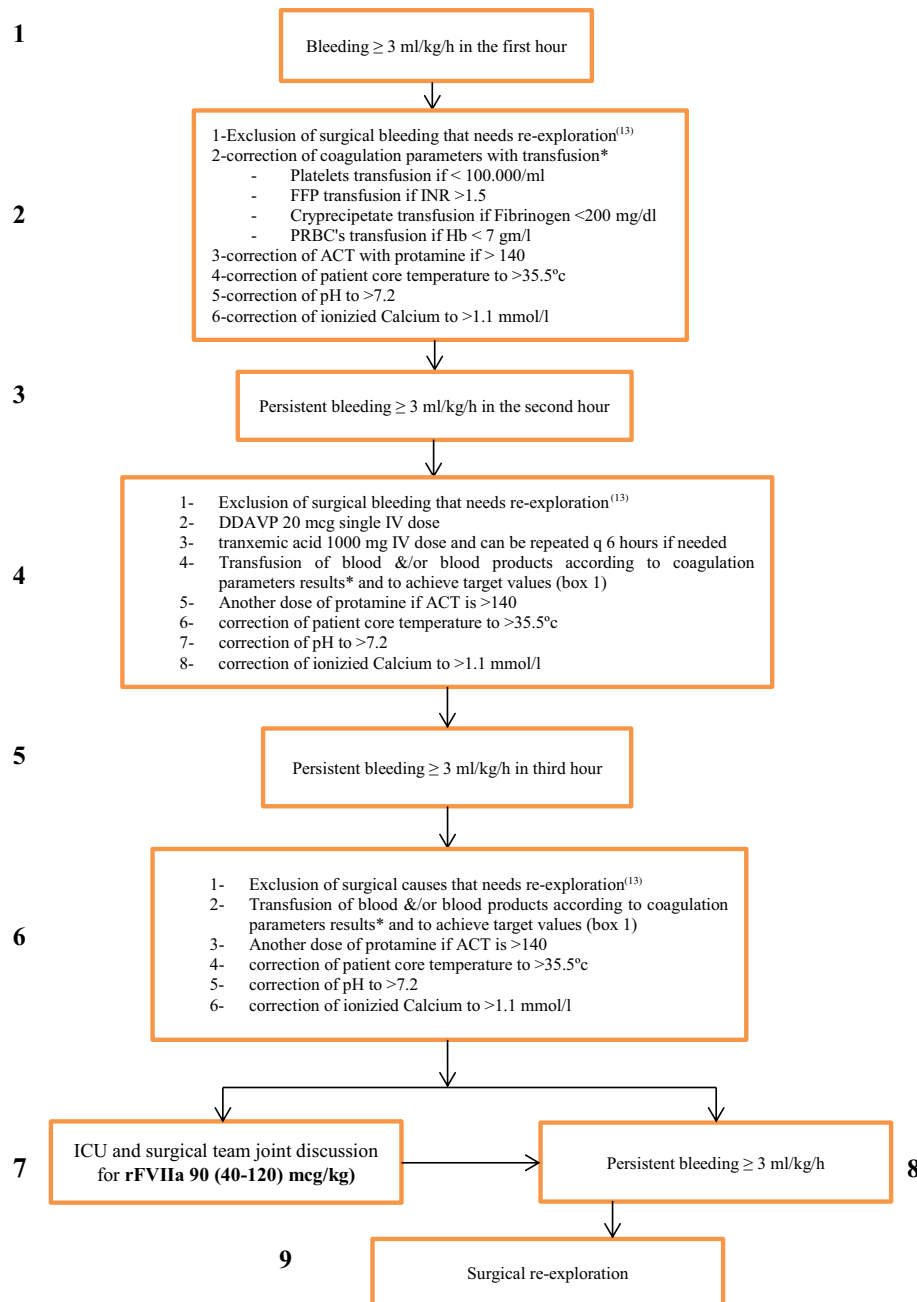


Figure 1. Management protocol for bleeding postoperative patients in Cardiac Surgical Intensive Care Unit. ^aTransfusion of blood products usually involved two to four units of platelets, two to four units of cryoprecipitate, one to two units of fresh frozen plasma, and one unit of packed red blood cells for each 1 g of Hb <7 g/L at a time. ACT = activated clotting time; FFP = fresh frozen plasma; ICU = intensive care unit; INR = International Normalized Ratio; IV = intravenous; PRBC = packed red blood cells; rFVIIa = recombinant factor VIIa.

to the ICU and every 2 hours until cessation of bleeding, then once daily and upon physician request.

The primary end points of this work were to compare both groups regarding: (1) the efficacy defined as: (a) the amount of bleeding from chest tube and (b) the amount of blood products transfused; and (2) the safety defined as incidence of thromboembolic adverse events (TAE) [cerebrovascular accidents (CVA), myocardial infarction (MI),

pulmonary embolism (PE), deep venous thrombosis, or arterial thrombosis]. Screening for TAE was performed by physical examination. If a TAE was suspected, color duplex sonography, transesophageal echocardiography, computed tomography scan, and laboratory tests were performed to confirm the diagnosis.

The secondary endpoints were to compare the two groups in regard to: (1) coagulation parameters; (2) the need of surgical re-exploration; (3)

incidence of acute renal impairment defined as increase of serum creatinine to >2 mg/dL or doubling the most recent preoperative creatinine level or a new requirement for dialysis postoperatively; (4) new incidence of pneumonia diagnosed if the patient had a new, persistent, or progressive lung infiltrate on chest radiograph and if at least two of the following criteria were present: temperature ≥ 38 °C, leukocytosis >12,000 cells/ μ L or leukopenia <3000 cells/ μ L, or purulent endotracheal secretions with a gram stain showing >25 neutrophils and <10 epithelial cells per field; (5) mediastinitis defined as a superficial or deep infection of the sternotomy wound with positive findings on cultures obtained from the wound; (6) days on mechanical ventilation; (7) CSICU and hospital length of stay; and (8) survival at 30 days postoperatively and at discharge.

Management of postoperative bleeding in CSICU and use of rFVIIa

Fig. 1 shows the protocol for the management of postoperative bleeding in our CSICU. Exclusion of surgical causes of bleeding that required re-exploration (cardiac tamponade, mediastinal hematoma, or large hemothorax) was done through clinical examination, hemodynamic monitoring, and radiographic tools including chest

X-ray and bedside echocardiography, together with the consultation of the attending cardiac surgeon [13]. The decision to administer rFVIIa was made after a discussion between the ICU and surgical teams regarding options for further treatments, the risks associated with rFVIIa or re-exploration, and hemodynamic state of the patient, according to the protocol in Fig. 1. The median rFVIIa dose used in our CSICU was 90 (interquartile range 40–120) mg/kg.

Statistical analysis

Summary statistics were presented as medians with ranges. Categorical variables are presented as counts and percentages. Group comparisons were done using Fisher’s exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. A *p* value ≤ 0.05 was considered significant in all tests. SPSS version 17 (SPSS Inc., Chicago, IL, USA) software was used to analyze the data.

Results

Demographic data

The medical records of 4856 patients who had cardiac surgery done in the period from February 2004 to December 2013 were reviewed. Four

Table 1. Demographic and surgical data of study patients.

	Control	rFVIIa	<i>p</i>
Age (y)	58 (21–78)	60 (24–73)	0.09
Weight	79 (48–102)	81 (46–113)	0.1
Male	133 (64.3)	146 (62.4)	0.69
Euro-score	7 (5–17)	8.5 (4–19)	0.21
Preoperative comorbidity			
Diabetes	53 (25.6)	64 (27.3)	0.74
Creatinine >1.4 mg/dL	68 (32.8)	71 (30.3)	0.61
LVEF <40%	39 (18.8)	51 (21.8)	0.48
Previous MI	44 (21.2)	43 (18.3)	0.47
Previous CVA	9 (4.3)	18 (7.6)	0.17
Pulmonary embolism	0 (0 %)	2 (0.9)	0.5
Emergency surgery	33 (15.9)	42 (17.9)	0.61
Redo surgery	89 (42.9)	113 (48.3)	0.3
Preop anticoagulant	58 (28)	73 (31.1)	0.6
Preop antiplatelet	123 (59.4)	131 (56)	0.5
Type of surgery			
Single valve	41 (19.8)	43 (18.4)	0.79
Multiple valves	63 (30.4)	81 (34.6)	0.36
CABG	48 (23.1)	40 (17.1)	0.15
CABG with valve(s)	39 (18.8)	36 (15.3)	0.37
Aortic surgery	11 (5.3)	20 (8.5)	0.2
Heart transplant	5 (2.4)	14 (6)	0.1
CPB time (min) ^a	127 (82–163)	129 (76–181)	0.2
Cross clamp time (min) ^a	92 (64–137)	98 (59–141)	0.18
Circulatory arrest time (min) ^a	19 (11–28)	23 (14–34)	0.2

Data are presented as *n* (%) or median (range). (min)^a minute, (y) years.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; CVA = cerebral vascular accident; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Preop = preoperation.

Table 2. Chest tube output in both treatment groups in the Cardiac Surgical Intensive Care Unit.

Time (h)	Control (mL/kg/h)	rFVIIa (mL/kg/h)	p
0-1 ^a	4.3 (3.1-6.9)	5.1 (3.6-7.4)	0.1
1-2	4.6 (3.8-7.1)	4.5 (3.5-7.9)	0.5
2-3	4.2 (3.3-6.8)	3.6 (2.9-7.1)	0.09
3-4	3.9 (3.1-5.6)	1.4 (1.0- 2.2)	0.004
4-5	3.4 (2.8-4.2)	1.3 (0.7-1.8)	0.009
5-6	2.8 (2.1-3.4)	1.0 (0.5-1.3)	0.03
6-7	2.5 (1.6-3.3)	0.8 (0.5-1.1)	0.03
7-8	1.9 (1.4-2.9)	0.8 (0.6-1.0)	0.05
8-9	1.9 (1.2-2.2)	0.6 (0.4-1.1)	0.04
9-12	1.1 (0.7-1.6)	0.3 (0.5-0.9)	0.08

Data are presented as median (range).
^a 0 hour is on admission.

Table 3. Blood products requirements of the treatment groups in the first 24 hours after admission to Cardiac Surgical Intensive Care Unit.

	Control (units)	rFVIIa (units)	p
FFP	8 (4-11)	3 (2-6)	0.006
Platelets	11 (5-17)	4 (2-8)	0.009
Cryoprecipitate	8 (4-13)	2 (0-4)	<0.001
PRBCs	6 (2-9)	2 (1-5)	0.01

Data are presented as median (range).
FFP = fresh frozen plasma; PRBCs = packed red blood corpuscles.

hundred and eighty-three patients (9.9%) were identified as having postoperative bleeding in CSICU. Eighteen patients were excluded due to receiving rFVIIa in the operating room, five for having corrective surgery for congenital heart disease, and 19 for being assisted with mechanical circulatory support. Two hundred and seven patients were included in the control group (received conventional treatment) and 234 patients were included in the rFVIIa group (received rFVIIa in addition to conventional treatment). There was no statistical significant difference in demographic and surgical characteristics of both groups (Table 1).

Primary endpoints

The median time from leaving the operating room until starting the rFVIIa was 187 (143-213) minutes. The chest tube output was high in both groups in the first 2 hours after admission to CSICU, and then it showed a significant drop in the rFVIIa group starting from 4 hours through 9 hours after admission compared with the control group (Table 2). The median number of blood product units used in the first 24 hours after admission to CSICU was statistically significant lower

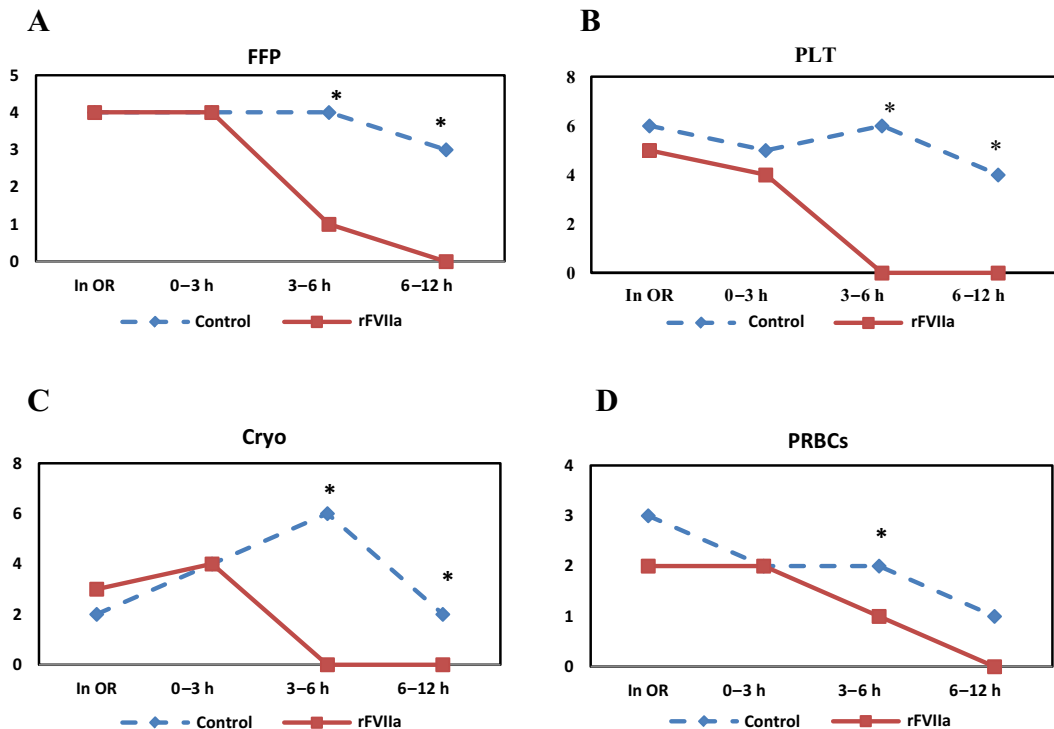


Figure 2. Median units of blood products requirements of the two groups. (A) Fresh frozen platelets (FFP); (B) platelets (PLT); (C) cryoprecipitate (Cryo); (D) packed red blood cells (PRBC). *p < 0.05. 0-3 hours = first 3 hours after Cardiac Surgical Intensive Care Unit admission (before recombinant factor VIIa administration); 3-6 hours = after admission to Cardiac Surgical Intensive Care Unit (all patients had received recombinant factor VIIa by this time); Group 1 = conventional treatment group; Group 2 = recombinant factor VIIa group; In OR = after disconnection of cardiopulmonary bypass until admission to Cardiac Surgical Intensive Care Unit; OR = operating room.

Table 4. Blood products requirements of both groups after the CPB and before admission to Cardiac Surgical Intensive Care Unit.

	In OR		p
	Control (units)	rFVIIa (units)	
FFP	4 (2-7)	4 (3-6)	0.8
Platelets	6 (3-12)	5 (2-9)	0.6
Cryoprecipitate	2 (0-6)	3 (2-8)	0.1
PRBCs	3 (1-5)	2 (1-6)	0.8

Data are presented as median (range).
FFP = fresh frozen plasma; OR = operating room; PRBCs = packed red blood corpuscles.

Table 5. Blood products requirements of both groups during the first 3 hours after admission to Cardiac Surgical Intensive Care Unit.

	0-3 h		p
	Control (units)	rFVIIa (units)	
FFP	4 (2-5)	4 (2-6)	0.9
Platelets	5 (2-10)	4 (2-7)	0.7
Cryoprecipitate	4 (0-6)	4 (2-4)	0.1
PRBCs	2 (2-3)	2(1-4)	0.5

Data are presented as median (range).
FFP = fresh frozen plasma; PRBCs = packed red blood corpuscles.

in the rFVIIa group compared with the control group (Table 3). Further analysis of the blood products transfused showed no significant difference between the two groups during the operating room, after discontinuation of CPB, and before transfer to CSICU (Table 4), or during the first 3 hours after admission to CSICU (Table 5). However, there were significant differences between the groups during the periods from 3 hours to 12 hours after CSICU admission (Tables 6 and 7; Fig. 2).

A total of 20 patients (4.5%) of all patients had thromboembolic complications. Seven (2.4%) patients in conventional treatment group (5 CVA and 2 MI) compared with 13 (5.5%) patients in the rFVIIa group (7 CVA, 5 MI, and 1 PE), $p = 0.27$.

Table 6. Blood products requirements of both groups from 3 hours to 6 hours after admission to Cardiac Surgical Intensive Care Unit.

	3-6 h		p
	Control (units)	rFVIIa (units)	
FFP	4 (1-6)	1 (0-1)	0.03
Platelets	6 (4-15)	0 (0-2)	0.001
Cryoprecipitate	6 (2-13)	0 (0-2)	0.008
PRBCs	2 (2-5)	1 (0-1)	0.04

Data are presented as median (range).
FFP = fresh frozen plasma; PRBCs = packed red blood corpuscles.

Table 7. Blood products requirements of both groups from 6 hours to 12 hours after admission to Cardiac Surgical Intensive Care Unit.

	6-12 h		p
	Control (units)	rFVIIa (units)	
FFP	3 (1-5)	0 (0-2)	0.009
Platelets	4 (0-4)	0	0.003
Cryoprecipitate	2 (0-8)	0	0.04
PRBCs	1 (0-2)	0 (0-1)	0.5

Data are presented as median (range).
FFP = fresh frozen plasma; PRBCs = packed red blood corpuscles.

Secondary endpoints

There were no statistical significant differences of the coagulation parameters between the two treatment groups on admission. However, the activated partial thromboplastin time, prothrombin time, activated clotting time, and international normalized ratio became statistically significant lower in the rFVIIa group 4 hours after admission when compared with the control group (Table 8). Eight patients in the rFVIIa group needed re-exploration compared with 19 patients in the conventional treatment group, $p = 0.011$. Five patients of both groups had aortic surgery, 12 had small arterial bleeder, one had injury at the CPB cannula site, and no specific cause of bleeding was found in nine patients. The number of mechanical

Table 8. Coagulation parameters of the treatment groups on admission to Cardiac Surgical Intensive Care Unit and 4 hours later.

	On admission		p	Post-treatment ^a		p
	Control (s)	rFVIIa (s)		Control (s)	rFVIIa (s)	
aPTT	50.3 (34.1-67.5)	50.8 (35.6-71.7)	0.58	48.2 (31.1-66.5)	43.8 (27.6-56.3)	0.03
PT	18.7 (12.7-24.4)	19.4 (11.5-26.3)	0.72	16.5 (10.8-20.7)	11.3 (10.3-14.1)	0.01
ACT	156 (142-174)	162 (134-186)	0.66	128.9 (113.2-134.7)	119.2 (109.8-127.3)	0.03
INR	1.52 (0.87-2)	1.49 (0.73-2.1)	0.54	1.34 (0.67-1.8)	1.26 (0.92-1.56)	0.05
Fibrinogen (mg/L)	234 (174-279)	226 (188-261)	0.81	257 (189-274)	251 (201-293)	0.74
Platelet ($\times 10^9$)	101 (54-210)	96 (46-198)	0.45	106 (49-207)	104 (54-203)	0.57

Data are presented as median (range). (s) seconds.
ACT = activated clotting time; aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time.
^a Four hours after admission to Cardiac Surgical Intensive Care Unit.

Table 9. Secondary endpoints of the treatment groups.

	Control	rFVIIa	<i>p</i>
Re-exploration	19 (9.3)	8 (3.4)	0.011
Renal failure	31 (14.9)	38 (16.2)	0.72
Dialysis	4 (1.9)	6 (2.5)	0.65
Pneumonia	11 (5.3)	17 (7.2)	0.4
Mediastinitis	6 (2.8)	9 (3.8)	0.58
Postop mechanical ventilation (d) ^a	11 (1–31)	8 (1–27)	0.06
CSICU stay (d) ^a	15 (1–41)	13 (1–36)	0.7
Hospital stay (d) ^a	41 (8–79)	38 (6–69)	0.8
30 mortality	5 (2.4)	5 (2.1)	0.84
Mortality at discharge	14 (6.7)	17 (7.2)	0.83

Data are presented as *n* (%) or median (range). (d)^a Days.
CSICU = Cardiac Surgical Intensive Care Unit; Postop = postoperation.

ventilator days were lower in rFVIIa, however, they were not significant compared with the other group. No statistical significant difference was noticed between the two groups regarding new onset renal failure, dialysis requirement, pneumonia, mediastinitis, CSICU, hospital length of stay, survival at 30-days postoperatively, and survival at discharge (Table 9).

Discussion

We observed a significant decrease in the chest tube bleeding, in the number of blood products units transfused, and a nonsignificant higher incidence of TAE among patients who received rFVIIa compared with the patients who received only conventional treatment.

Four hundred and eighty three (9.9%) of our patients had postoperative bleeding, which is a relatively high percentage compared with other centers; however, this can be explained by the type of our patients (with a high European System for Cardiac Operative Risk Evaluation II score ranging between 7 and 9, 50% were a redo, 15% had emergency surgery, and 30% had preoperative anticoagulation).

Although originally conceived as a treatment for hemorrhage in hemophiliacs, this report suggests that rFVIIa may be of benefit when given to cardiac surgery patients who develop severe refractory blood loss. There is a clinical sentiment that rFVIIa decreases bleeding. Several studies, reviews, and meta-analysis have reported the role of rFVIIa in controlling bleeding postcardiac surgery [5–10,14–30].

The bleeding in the two treatment groups was comparable in the first hours after admission to CSICU, and then with the start of rFVIIa administration (around 3 hours after admission) there was a statistically significant drop in the bleeding from the rFVIIa group which continued until the bleeding in the other group was almost controlled

after 9 hours from admission. Also there was a nonsignificant difference in the number of blood product units transfused in the operating room and in the first 3 hours in CSICU (before the administration of rFVIIa). Taken together, this decrease in chest tube bleeding can be clearly attributed to the direct effect of rFVIIa.

In 2011, The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists updated the Blood Conservation Clinical Practice Guidelines stating that: use of rFVIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB Class Iib [31].

Although rFVIIa is being increasingly used, only two randomized controlled trials examined its use in cardiac surgery in adults: Gill et al. [14] in a randomized placebo controlled trial showed that significantly fewer patients in the FVIIa group underwent a reoperation as a result of bleeding or required allogenic transfusion. Also, there were more critical serious adverse events in the FVIIa group, although not statistically significant. For the first time, a hemostatic agent has the possibility of being an effective alternative to allogeneic transfusion in cardiac surgery patients with uncontrolled postoperative bleeding. Disprose et al. [6] showed in another pilot study that rFVIIa significantly reduces the need for allogeneic transfusion in complex noncoronary cardiac surgery without causing adverse events. However, when the results were analyzed by intention to treat, the results were negative.

Karkouti et al. [15] published the largest study analyzing the effect of rFVIIa to control refractory bleeding after cardiac surgery. The study compared 114 patients treated with rFVIIa versus 541 patients not treated with rFVIIa. The results confirmed that rFVIIa significantly reduces the hemorrhage and the transfusion requirements without causing adverse effects; furthermore,

emphasizing that early treatment is associated with better clinical progress.

However, many retrospective data analyses and systemic reviews [32–40] concluded that the use of rFVIIa as a rescue therapy has met with mixed results. Although showing an overall benefit for the application of rFVIIa, serious inherent publication bias associated with these reports does not support its use, at least when employed prophylactically. Also it did not show any effect on mortality and may substantially increase the risk for thromboembolic events.

In our report, TAEs were not significantly higher in the FVIIa group compared with the control group (5.5% vs. 2.4%, $p = 0.27$). Around 25% of patients in both groups had preoperative TAE (CVA, MI, or PE). This makes them a higher risk. In addition, preoperative carotid duplex is not a routine preoperative investigation, which if done could have identified at-risk patients.

The main complication associated with rFVIIa is thrombosis. In a systematic review [39] that focused on the efficacy and safety of rFVIIa, the incidence rate of thrombosis was 1–2%. Dunkley et al. [41] reported an associated thromboembolic rate in 4% of patients. Cardiac surgery patients represent high-risk categories for systemic or localized thrombosis after rFVIIa. The incidence of TAEs in our study is comparable to others [42]. Our patients had a relatively long CPB time which can cause a more severe abnormality of coagulation causing postoperative bleeding associated with disseminated intravascular coagulation and thrombosis when rFVIIa is used.

By contrast, Levi et al. [40] found an increased risk of arterial thromboembolic events among patients who received off-label rFVIIa as compared with patients who received placebo for bleeding episodes. Analysis of the rates of arterial thromboembolism events according to the type of bleeding showed that these rates were not significantly higher in cardiac surgery bleeding, possibly because of the lower number of patients included.

Zatta et al. [43] found that the overall unadjusted thromboembolic adverse events rate was 10.9%, with 48% of all TAEs occurring in cardiac surgery patients. The majority of TAEs were arterial (6.3%). They stated that in the absence of a suitable control group, it is difficult to draw any meaningful conclusions on the overall rate of TAEs reported to the registry.

In a case-control study using Australian and New Zealand Hemostasis Registry patients and a comparable group of patients from the

Australasian Society for Cardiac and Thoracic Surgeons database, Mitra et al. [44] found no increase in stroke or MI associated with the use of rFVIIa.

Our results showed a significant improvement in most of the coagulation parameters when measured 4 hours after admission to CSICU in the rFVIIa group compared with the control group. Fibrinogen showed an increase which was insignificantly different between the two study groups. This could be explained by the significantly excessive transfusion of fresh frozen plasma and cryoprecipitate in conventional treatment group compared to rFVIIa group which increased the fibrinogen level in this group more than the rFVIIa group.

Our results show that eight patients needed re-exploration after rFVIIa administration compared with 19 patients in the control group, $p = 0.011$. This relatively low incidence of re-exploration in the FVIIa group can be explained—in addition to the role of rFVIIa—by: (1) exclusion of surgical causes of bleeding was worked out many times before the administration of the drug; (2) rFVIIa efficacy has been studied predominantly after the patients had already received significant volumes of blood products and antifibrinolytics (tranexemic acid and desmopressin) prior to treatment [25]. However, it has rarely been studied in isolation.

Uber et al. [20] concluded that rFVII administration in the ICU appears comparable with reoperation for refractory bleeding after complex cardiovascular surgical procedures and might represent an alternative to reoperation in selected patients.

Von Heymann et al. [7] found that the survival rates after 6 months were similar in his study groups which can be related to the delay in the decision to using rFVIIa and to the fact that patients had worsened. An important contribution of his study [7] is the new concept of the “ideal” time in which rFVIIa should be used. Previous studies had considered that rFVIIa as the last therapeutic alternative to be used when other resources had failed. The median time from leaving the operating room until the administration of rFVIIa in our patient groups was almost 3 hours, including the time needed for preparation of the drug by the pharmacy which is around 30 minutes.

The limitations of our study can be summarized into the following. Firstly, being a retrospective study, most findings should be viewed as associative rather than causative, and may be affected by

unmeasured confounders and provide the template for larger prospective evaluations of this agent. Secondly, the number of bleeding patients who received rFVIIa in our study was large (53.1% of the whole patient population). This can be explained by many factors: the whole cost for all medical procedures is free to the patient once he is eligible to be treated in this institution, so making the decision is easier and there are no financial consequences to the patients or to the prescribing physician. Thirdly, the wide range of rFVIIa dose used in our CSICU may be due to the considerable heterogeneity among the patients; baseline risk, surgical complexity, condition at time of rFVIIa therapy (e.g., amount and rate of blood loss, hemodynamic status, organ compromise). The decision to give rFVIIa involved mostly the surgeon and the intensivist, but did not involve the clinical pharmacist or the hematologist. The easy access to order the medication is also another factor as the attending intensivist and/or the surgeon alone is eligible to prescribe the medication according to hospital policies. Fourthly, although treatment with rFVIIa was guided by a firm institutional clinical protocol that involved correction of coagulation, pH, temperature, and ionized calcium, a point of care system involving the thromboelastography would have allowed a more accurate evaluation of the overall clotting process and which blood product and/or hemostatic agents, such as rFVIIa, would be needed [45]. Recently, we have introduced thromboelastography in our CSICU. However, the training is still in evolution on the view of the inconclusive results that we get sometimes. The time needed to order and prepare the specific blood product after the interpretation of the thromboelastogram results is still long (at least 30 minutes) which makes the application of these results to the protocol for the management of a bleeding patient more difficult.

Nevertheless, to our knowledge, this is the largest study including a continuous series of patients treated at a single institution according to standardized clinical protocol that study the efficacy and safety of rFVIIa in post cardiac surgical bleeding.

Conclusion

FVIIa can be effective in controlling intractable postoperative cardiac surgical bleeding and reducing blood products transfused and re-exploration rate; however, with nonsignificant higher TEA events and no morbidity or survival

benefit. Being an expensive medication, application of a point-of-care protocol will help to better choose the patients that will benefit FVIIa and reduce the cost. Further prospective randomized studies are needed to confirm these findings.

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References

- [1] Herwaldt LA, Swartzendruber SK, Zimmerman MB, Scholz DA, Franklin JA, Caldaroni CA. Hemorrhage after coronary bypass graft procedures. *Infect Control Hosp Epidemiol* 2003;24:44–50.
- [2] Taylor GJ, Mikell FL, Moses HW, Dove JT, Katholi RE, Malik SA, et al. Determinants of hospital charges for coronary artery bypass surgery: the economic consequences of postoperative complications. *Am J Cardiol* 1990;65:309–13.
- [3] Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008;358:1229–39.
- [4] Dixon B, Santamaria JD, Reid D, Collins M, Rechnitzer T, Newcomb AE, et al. The association of blood transfusion with mortality after cardiac surgery: cause or confounding? *Transfusion* 2013;53:19–27.
- [5] Karkouti K, Beattie WS, Wijeyesundera DN, Yau TM, McCluskey SA, Ghannam M, et al. Recombinant factor VIIa for intractable blood loss after cardiac surgery: A propensity score-matched case-control analysis. *Transfusion* 2005;45:26–34.
- [6] Diprose P, Herbertson MJ, O'Shaughnessy D, Gill RS. Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study. *Br J Anaesth* 2005;95:596–602.
- [7] Von Heymann C, Redlich U, Jain U, Kastrop M, Schroeder T, Sander M, et al. Recombinant activated factor VII for refractory bleeding after cardiac surgery—a retrospective analysis of safety and efficacy. *Crit Care Med* 2005;33:2241–6.
- [8] Gelsomino S, Lorusso R, Romagnoli S, Bevilacqua S, De Cicco G, Billè G, et al. Treatment of refractory bleeding after cardiac operations with low-dose recombinant activated factor VII (NovoSeven): a propensity score analysis. *Eur J Cardiothorac Surg* 2008;33:64–71.
- [9] Tritapepe L, De Santis V, Vitale D, Nencini C, Pellegrini F, Landoni G, et al. Recombinant activated factor VII for refractory bleeding after acute aortic dissection surgery: a propensity score analysis. *Crit Care Med* 2007;35:1685–90.
- [10] Zangrillo A, Mizzi A, Biondi-Zoccai G, Bignami E, Calabrò MG, Pappalardo F, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2009;23:34–40.
- [11] Hedner U. Recombinant factor VIIa (Novoseven) as a hemostatic agent. *Semin Haematol* 2001;38(Suppl. 12):43–7.

- [12] Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734-45.
- [13] Kouchoukos Nicholas T, Blackstone Eugene H, Hanley Frank L, Kirklin James K, Barratt-Boyes BG. *Cardiac surgery expert consult*. 4th ed. Philadelphia: Elsevier Saunders; 2013.
- [14] Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009;120:21-7.
- [15] Karkouti K, Yau T, Riazi S, Dattilo KM, Wasowicz M, Meineri M, et al. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. *Can J Anaesth* 2006;53:802-9.
- [16] Romagnoli S, Bevilacqua S, Gelsomino S, Pradella S, Ghilli L, Rostagno C, et al. Small-dose recombinant activated factor VII (NovoSeven) in cardiac surgery. *Anesth Analg* 2006;102:1320-6.
- [17] Bishop CV, Renwick WEP, Hogan C, Haeusler M, Tuckfield A, Tatoulis J. Recombinant activated factor VII: Treating postoperative hemorrhage in cardiac surgery. *Ann Thorac Surg* 2006;81:875-9.
- [18] McCall P, Story DA, Karapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. *Can J Anaesth* 2006;53:926-33.
- [19] Karkouti K, Beattie WS, Arellano R, Aye T, Bussieres JS, Callum JL, et al. Comprehensive Canadian review of the off-label use of recombinant activated factor VII in cardiac surgery. *Circulation* 2008;118:331-8.
- [20] Uber WE, Toole JM, Stroud MR, Haney JS, Lazarchick J, Crawford Jr FA, et al. Administration of recombinant activated factor VII in the intensive care unit after complex cardiovascular surgery: clinical and economic outcomes. *J Thorac Cardiovasc Surg* 2011;141:1469-77.
- [21] Masud F, Bostan F, Chi E, Pass SE, Samir H, Stuebing K, et al. Recombinant factor VIIa treatment of severe bleeding in cardiac surgery patients: a retrospective analysis of dosing, efficacy, and safety outcomes. *J Cardiothorac Vasc Anesth* 2009;23:28-33.
- [22] Bowman L, Uber W, Stroud M, Christiansen LR, Lazarchick J, Crumbley 3rd AJ, et al. Use of recombinant activated factor VII concentrate to control postoperative hemorrhage in complex cardiovascular surgery. *Ann Thorac Surg* 2008;85:1669-77.
- [23] Hacquard M, Durand M, Lecompte T, Boini S, Briançon S, Carteaux JP. Off-label use of recombinant activated factor VII in intractable hemorrhage after cardiovascular surgery: an observational study of practices in 23 French cardiac centers (2005-7). *Eur J Cardiothorac Surg* 2011;40:1320-7.
- [24] Alfirevic A, Duncan A, You J, Lober C, Soltesz E. Recombinant factor VII is associated with worse survival in complex cardiac surgical patients. *Ann Thorac Surg* 2014;98:618-24.
- [25] Rao V, Lobato R, Bartlett B, Klanjac M, Mora-Mangano CT, Soran PD, et al. Factor VIII inhibitor bypass activity and recombinant activated factor VII in cardiac surgery. *J Cardiothorac Vasc Anesth* 2014;28:1221-6.
- [26] Raivio P, Suojaranta-Ylinen R, Kuitunen AH. Recombinant factor VIIa in the treatment of postoperative hemorrhage after cardiac surgery. *Ann Thorac Surg* 2005;80:66-71.
- [27] Koncar IB, Davidovic LB, Savic N, Sindelić RB, Ilić N, Dragas M, et al. Role of recombinant factor VIIa in the treatment of intractable bleeding in vascular surgery. *Vasc Surg* 2011;53:1032-8.
- [28] Yan W, Xuan C, Ma G, Zhang L, Dong N, Wang Z, et al. Combination use of platelets and recombinant activated factor VII for increased hemostasis during acute type a dissection operations. *J Cardiothorac Surg* 2014;9:156-64.
- [29] Andersen ND, Bhattacharya SD, Williams JB, Fosbol EL, Lockhart EL, Patel MB, et al. Intraoperative use of low-dose recombinant activated factor VII during thoracic aortic operations. *Ann Thorac Surg* 2012;93:1921-9.
- [30] Goksedef D, Panagopoulos G, Nassiri N, Levine RL, Hountis PG, Plestis KA. Intraoperative use of recombinant activated factor VII during complex aortic surgery. *J Thorac Cardiovasc Surg* 2012;143:1198-204.
- [31] The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. *Ann Thorac Surg* 2011;91:944-82.
- [32] Willis C, Bird R, Mullany D, Cameron P, Phillips L. Use of rFVIIa for critical bleeding in cardiac surgery: dose variation and patient outcomes. *Vox Sang* 2010;98:531-7.
- [33] Donovan PJ, Iedema J, McLeod DS, Kubler P, Pillars N. Off-label use of recombinant factor VIIa in two tertiary hospitals in Queensland. *ANZ J Surg* 2012;83:149-54.
- [34] AlGahtani F, Alshaika M, AlDiab A. Recombinant activated factor VII in controlling bleeding in nonhemophilic patients. *Ann Saudi Med* 2010;30:198-202.
- [35] Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011;154:529-40.
- [36] Hardy JF, Belisle S, Van der Linden P. Efficacy and safety of activated recombinant factor VII in cardiac surgical patients. *Curr Opin Anaesthesiol* 2009;22:95-9.
- [37] Hardy JF, Belisle S, Van der Linden P. Efficacy and safety of recombinant activated factor VII to control bleeding in nonhemophilic patients: a review of 17 randomized controlled trials. *Ann Thorac Surg* 2008;86:1038-48.
- [38] Iau P, Ong V, Tze W, Koh PL, Hartman M. Use of activated recombinant factor VII in severe bleeding—evidence for efficacy and safety in trauma, postpartum hemorrhage, cardiac surgery, and gastrointestinal bleeding. *Transfus Med Hemother* 2012;39:139-50.
- [39] Levi M, Peters M, Büller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. *Crit Care Med* 2005;33:883-90.
- [40] Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010;363:1791-800.
- [41] Dunkley S, Phillips L, Mc Call P, Brereton J, Lindeman R, Jankelowitz G, et al. Recombinant activated factor VII in cardiac surgery: experience from the Australian and New Zealand Haemostasis Registry. *Ann Thorac Surg* 2008;85:836-44.
- [42] Warren O, Mandal K, Hadjianastassiou V, Knowlton L, Panesar S, John K, et al. Recombinant activated factor VII in cardiac surgery: a systematic review. *Ann Thorac Surg* 2007;83:707-14.
- [43] Zatta A, McQuilten Z, Kandane-Rathnayake R, Isbister J, Dunkley S, Mcneil J, et al. The Australian and New Zealand Hemostasis Registry: ten years of data on off-licence use of recombinant activated factor VII. *Blood Transfus* 2015;13:86-99.
- [44] Mitra B, Phillips L, Cameron P, Billah B, Reid C. The safety of recombinant factor VIIa in cardiac surgery. *Anaesth Intensive Care* 2010;38:671-7.
- [45] Luddington RJ. Thrombelastography/thromboelastometry. *Clin Lab Haematol* 2005;27:81-90.