

Comparison of low- and high-dose recombinant activated factor VII for postcardiac surgical bleeding

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Abstract

Aim of the Study: A retrospective observational study to compare safety and efficacy of high and low doses of recombinant activated factor VIIa (rFVIIa) in severe postcardiac surgical bleeding. **Patients and Methods:** From 2004 to 2014, all patients who received rFVIIa for bleeding after cardiac surgery were included and arranged in two groups; Group 1: Low dose (40–50 mcg/kg) ($n = 98$) and Group 2: High dose (90–120 mcg/kg) ($n = 156$). **Results:** There was no significant difference in demographic and surgical characteristics of both groups on admission to Cardiac Surgical Intensive Care Unit (CSICU). There was no significant difference between the two groups regarding the reduction in chest tube bleeding in the first 6 h or the transfusion requirement in the 24 h after admission to CSICU. A total of 15 patients (5.9%) had thromboembolic adverse events. (Seven (7.1%) patients in Group 1 compared to 8 (5.1%) patients in Group 2, $P = 0.58$). There were no significant differences in all-cause mortality at 30 days (2% in Group 1 vs. 3.2% in Group 2, $P = 0.6$) and at hospital discharge between the two study groups (6.1% in Group 1 vs. 8.3% in Group 2, $P = 0.5$), respectively. There was no significant difference between the two groups regarding the need for re-exploration, days on mechanical ventilation, CSICU, or hospital stay. **Conclusion:** In this report, Low-dose rFVIIa showed equivalent efficacy and safety to high-dose rFVIIa. Further prospective randomized studies are needed to confirm these findings.

Keywords: Bleeding, cardiac surgery, low dose, recombinant activated factor VIIa

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Introduction

Severe bleeding occurs in 10%–15% of patients undergoing cardiac surgical procedures.^[1-3] This small subset of the cardiac surgical population, account for 80% of all blood products transfused during cardiac surgery.^[4,5] Many require massive transfusion and/or re-exploration, both of which are associated with marked increases in morbidity and mortality.^[2,6,7]

The use of hemostatic rescue agents, such as recombinant activated factor VIIa (rFVIIa; Novo Nordisk, Bagsvaerd, Denmark), has been accepted for achieving hemostasis when conventional therapy has failed. Many studies have reported that rFVIIa is a safe and effective treatment for hemorrhage after cardiac surgery.^[8-10] However, a clear benefit-risk profile for the use of agents such as rFVIIa is lacking.^[11-14]

The optimal dosing regimen for rFVIIa in the postcardiac surgical setting remains unclear. The

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reported dose range for single bolus administration has been broad (11.1–180 mcg/kg). Recommendations made by various expert panels have suggested doses in the order of 40–100 mcg/kg in the setting of uncontrolled postcardiac surgical hemorrhage,^[8] and the use of a low dose has been accepted in most institutions.^[15,16]

rFVIIa dosage is not based on and cannot be monitored by available laboratory testing. Coagulation tests such as the prothrombin time and activated partial thromboplastin time are reported to be shortened *in vitro* this may not reflect *in vivo* effect of the drug on the patients' coagulation system at their own body temperature. The conventional measurement of FVIIa in the plasma after rFVIIa administration only proves the presence of FVIIa and its successful administration but does not predict any effect on hemostasis.^[17] This makes the only available way to study rFVIIa and determine its appropriate dose is through the effect on outcomes such as a decrease in bleeding, transfusion requirement, and surgical reexploration. This is not fully representative since these effects involve other coagulation system components as well.

The aim of this work is to show the difference in safety and efficacy between both low and high doses of rFVIIa when given to patients with severe postcardiac intractable surgical bleeding at the end of a step-by-step protocol to control bleeding at our institute.

Patients 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, Saudia Arabia.

Patients

Retrospectively, the medical charts of all adult patients who had cardiac surgery in the period between January 2004 and December 2014 were screened for the administration of rFVIIa for postoperative bleeding in the Intensive Care Unit (ICU) ($n = 287$). Patients who were < 18-year-old, pregnant females, have a history of primary coagulation defect, had a history of peripheral vascular disease, received rFVIIa in the operating room, having surgery for corrections of congenital heart diseases, requiring mechanical circulatory support, were excluded ($n = 33$) from the study. All patients who received rFVIIa in the Cardiac Surgical ICU (CSICU) for postoperative bleeding ($n = 254$) were included in the study. The patients were arranged in two groups according to the dose of rFVIIa given to them, Group 1: Low dose (40–50 mcg/kg) ($n = 98$) and Group 2: High dose (90–120 mcg/kg) ($n = 156$).

The study protocol was approved by the Institutional Research Center and Ethics Committees (RAC #2121076). Being retrospective chart review study, consent was waived by the ethical committee.

Patients' demographics, preoperative comorbidities, preoperative anticoagulation, priority of surgery, type of surgery, cardiopulmonary bypass time, 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.^[18]

The primary endpoints of this work were to compare both groups regarding:

1. The efficacy defined as:
 - a. The amount of bleeding from chest tube
 - b. The amount of blood products transfused.
2. The safety defined as the incidence of new thromboembolic adverse events (TAE) (cerebrovascular accidents [CVA], myocardial infarction [MI], pulmonary embolism [PE], deep venous thrombosis [DVT], 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

The secondary endpoints to compare both groups were regarding the following points:

1. All-cause mortality at 30 days postoperatively and at discharge
2. The incidence of surgical re-exploration
3. The need for multiple doses of rFVIIa
4. Days on mechanical ventilation
5. Length of stay (LOS) in ICU and hospital.

Management of postoperative bleeding in Cardiac Surgical Intensive Care Unit and use of recombinant activated factor VIIa

Figure 1 shows the protocol for management of postoperative bleeding in our CSICU. Exclusion of surgical causes of bleeding that requires 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 attending cardiac surgeon. The usual dose of rFVIIa used in our CSICU is either; a full dose (90–120 mcg/kg) or a half dose (40–50 mcg/kg). Decision to administer either doses of rFVIIa was made after

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 Figure 1. If a repeat dose of rFVIIa was needed, it would be of the same concentration as the first one.

Statistical analysis

Summary statistics is presented as medians with interquartile ranges. Group comparisons are done using Mann-Whitney U-test for continuous variables, and Fisher’s exact test for categorical variables. All tests, $P \leq 0.05$ is considered statistically significant. Kaplan-Meier survival curve was estimated, and comparison between overall survivals in the two groups was done using log-rank test. Type 1 error rate was set at 5%. SPSS version 17 (SPSS Inc, Chicago, Illinois). software was used to analyze the data.

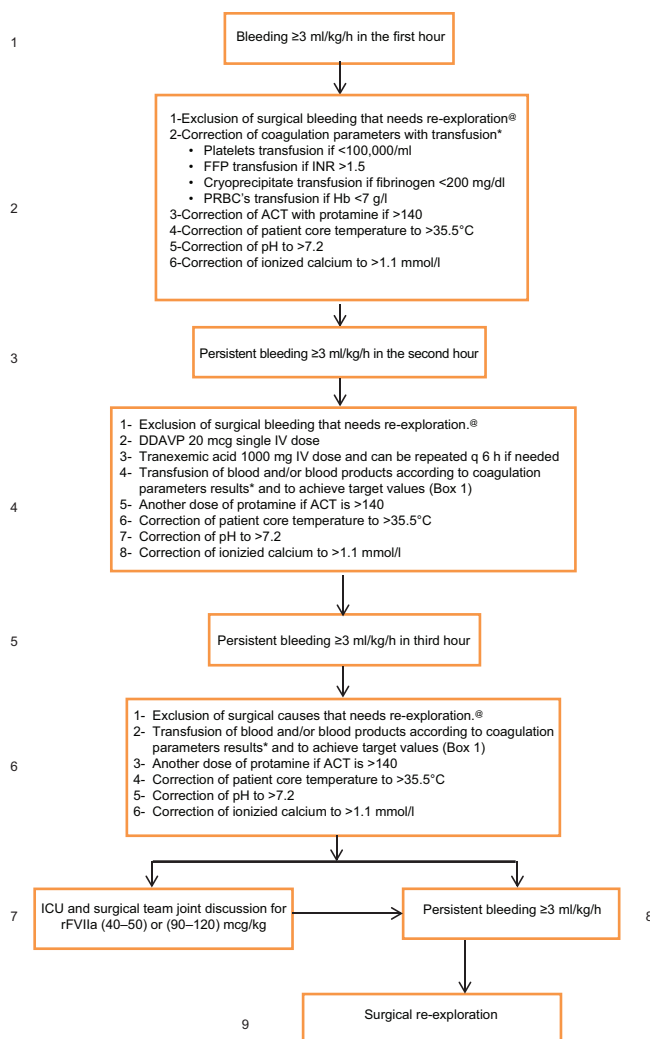


Figure 1: Management protocol for bleeding postoperative patients in CSICU. @Exclusion of surgical bleeding that needs re-exploration according to Kirklin/ Barratt-Boys, 2013 [31]. *Transfusion of blood products usually involved 2–4 units of platelets, 2–4 units of cryoprecipitate, 1–2 units of fresh frozen plasma, and 1 unit of packed red blood corpuscles for each 1 g of hemoglobin <7 g/L at a time

Results

The medical records of all adult patients who had cardiac surgery done in the period from January 2004 to December 2014 were reviewed. Two hundred and eighty-seven patients were identified to have received rFVIIa for postoperative bleeding in CSICU.

Twenty-two patients were excluded due to rFVIIa administration in the operating room before CSICU admission. This administration of rFVIIa in the operating room was mainly based on the surgeon and anesthetist decision and not following the protocol in Figure 1. Three patients were also excluded for having corrective surgery for congenital heart disease, and 8 for being assisted with mechanical circulatory support. Ninety-eight patients were included into Group 1 (low-dose rFVIIa; 40–50 mcg/kg), and 156 patients were included into Group 2 (high-dose rFVIIa; 90–120 mcg/kg). There was no statistically significant difference in demographic and surgical characteristics of both groups [Table 1].

Primary endpoints

There was no statistically significant difference between the two groups regarding the reduction in chest tube bleeding in the first 6 h after admission to CSICU

Table 1: Demographic and surgical characteristics of both treatment groups on admission to Cardiac Surgical Intensive Care Unit

	Group 1 (98)	Group 2 (156)	P
Age (years) [§]	59 (31-77)	61 (26-72)	0.7
Weight (kg) [§]	85 (52-112)	81 (49-107)	0.8
Male, n (%)	63 (64.3)	97 (62.2)	0.8
Euro-score [§]	6.5 (4-17)	8 (4-19)	0.3
Preoperative comorbidity, n (%)			
Diabetes	30 (30.6)	39 (25)	0.38
Creatinine > 1.4 mg/dl	28 (28.5)	52 (33.3)	0.49
LVEF <40%	22 (22.4)	32 (20.5)	0.75
Previous MI	19 (19.3)	26 (16.6)	0.6
Previous CVA	11 (11.2)	8 (5.1)	0.09
Pulmonary embolism	2 (2)	0 (0)	0.14
Emergency surgery	24 (24.4)	25 (16)	0.1
Redo surgery	50 (51)	69 (44.2)	0.3
Preoperative anticoagulant	38 (38.7)	46 (29.5)	0.13
Preoperative antiplatelet	59 (60.2)	85 (54.5)	0.4
Type of surgery, n (%)			
Single valve	23 (23)	28 (17.9)	0.33
Multiple valves	40 (40.8)	47 (30.1)	0.1
CABG	23 (23.5)	22 (14.1)	0.07
CABG with valve (s)	22 (22.4)	20 (12.8)	0.06
Aortic surgery	4 (4.1)	17 (10.9)	0.2
Heart transplant	2 (2)	12 (7.7)	0.09
CPB time (min) [§]	121 (71-167)	133 (69-176)	0.4
Cross clamp time (min) [§]	84 (53-119)	106 (62-153)	0.6
Circulatory arrest time (min) [§]	17 (13-28)	23 (15-36)	0.1

[§]Median and range, n (%). CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass grafting; CVA: Cerebrovascular accident; MI: Myocardial infarction; LVEF: Left ventricular ejection fraction

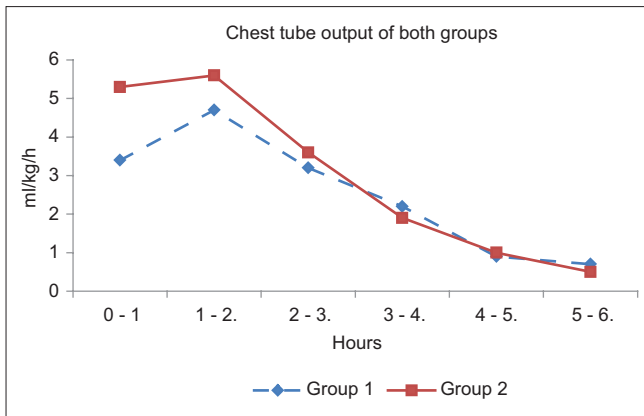


Figure 2: Chest tube output of both treatment groups in the first 6 h after admission to Cardiac Surgical Intensive Care Unit. No statistically significant difference between the two groups

[Table 2 and Figure 2]. The transfusion requirement also did not show statistically significant difference between the two groups in the first 24 h after CSICU admission [Table 3].

A total of 15 patients (5.9%) had TAEs. Seven (7.1%) patients in Group 1 (4 CVA and 3 MI) compared to 8 (5.1%) patients in Group 2 (3 CVA, 3 MI, 1 PE and 1 DVT), $P = 0.58$.

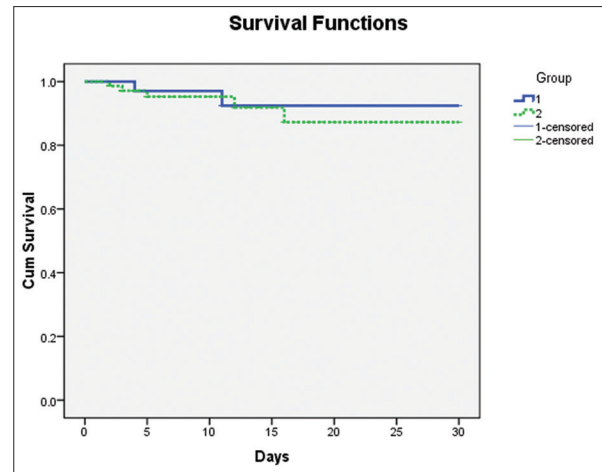
Secondary endpoints

There were no statistically significant differences of all-cause mortality at 30 days (2 [2%] in Group 1 vs. 5 [3.2%] in Group 2, $P = 0.6$) and at hospital discharge between the two study groups (6 [6.1%] in Group 1 vs. 13 [8.3%] in Group 2, $P = 0.5$), Figures 3 and 4, respectively. There was no statistically significant difference between the two groups regarding the incidence of re-exploration, need for multiple rFVIIa doses, and days on mechanical ventilation, CSICU, or hospital LOS [Table 4].

Discussion

In this report, the off-label low dose of rFVIIa (40–50 mcg/kg) was studied against the high dose (90–120 mcg/kg) in patients who had intractable postcardiac surgical bleeding. We did not observe any statistically significant difference between the two groups regarding the amount of chest tube bleeding in the first 6 h after CSICU admission, the number of blood products units transfused in the first 24 h, new incidence of TAE, mortality at 30 days and at hospital discharge, need for re-exploration, days on mechanical ventilation, need for multiple doses, CSICU, or hospital LOS.

A few have reports compared the low-dose rFVIIa to conventional treatment of blood products and factors.



Overall comparisons			
	χ^2	df	Significant
Log rank (Mantel-Cox)	0.232	1	0.630
Breslow (generalized Wilcoxon)	0.281	1	0.596
Tarone-Ware	0.246	1	0.620

Test of equality of survival distributions for the different levels of group

Figure 3: Thirty days mortality. Kaplan–Meier curve for survival among the two groups at 30 days after surgery

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

	Group 1	Group 2	P
0-1 h [§] (ml/kg/h)	4.7 (3.3-6.7)	5.3 (3.8-7.4)	0.1
1-2 h [§] (ml/kg/h)	4.3 (3.4-7.2)	4.8 (3.7-6.2)	0.3
2-3 h [§] (ml/kg/h)	3.4 (2.1-5.8)	3.7 (2.5-6.5)	0.9
3-4 h [§] (ml/kg/h)	1.2 (1.6-2.2)	1.4 (1.2-2.1)	0.5
4-5 h [§] (ml/kg/h)	0.9 (0.3-1.8)	1 (0.6-1.7)	0.8
5-6 h [§] (ml/kg/h)	0.7 (0.5-0.9)	0.5 (0.2-0.8)	0.7

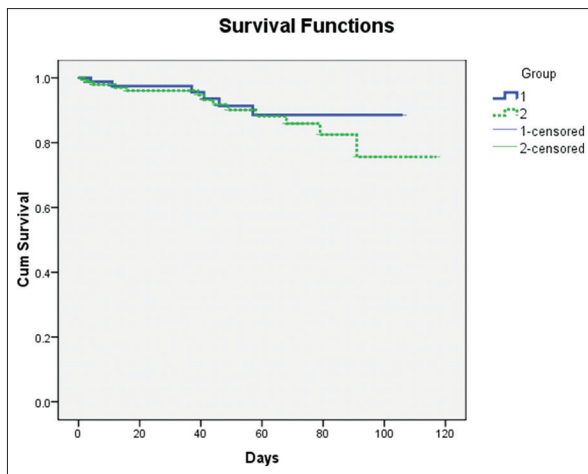
[§]Median and range, 0 h is on admission

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

	Group 1	Group 2	P
FFP (units) [§]	4 (2-8)	3 (2-6)	0.9
Platelets (units) [§]	2 (2-8)	4 (2-6)	0.3
Cryoprecipitate (units) [§]	2 (2-4)	2 (0-4)	0.5
PRBCs (units) [§]	2 (0-3)	3 (1-5)	0.7

[§]Median and range. FFP: Fresh frozen plasma; PRBCs: Packed red blood corpuscles

Brase *et al.*^[19] showed that low dose (median dose was 12 mcg/kg, with a range of 3–62 mcg/kg) and early administration of rFVIIa was associated with significant increase in ventilator days, ICU LOS, but not inferior to standard therapy of blood and factor administration in reexploration rate. There was no increase in the risk of thromboembolism or acute kidney injury associated with rFVIIa administration. However, the definition of the bleeding they used is different from ours. The finding that rFVIIa patients received more blood product



Overall comparisons

	χ^2	df	Significant
Log rank (Mantel-Cox)	0.535	1	0.465
Breslow (generalized Wilcoxon)	0.276	1	0.600
Tarone-Ware	0.341	1	0.559

Test of equality of survival distributions for the different levels of group

Figure 4: Mortality at discharge. Kaplan–Meier curve for survival among the two groups at discharge from hospital

Table 4: Secondary endpoints of the treatment groups

	Group 1	Group 2	P
Re-exploration, n (%)	4 (4.1)	5 (3.2)	0.74
Multiple doses, n (%)	4 (4.1)	3 (1.9)	0.43
Postoperative mechanical ventilation (days) [§]	6 (2-18)	8 (1-32)	0.3
CSICU stay (days) [§]	14 (2-35)	12 (2-40)	0.4
Hospital stay (days) [§]	39 (10-72)	35 (8-67)	0.09

[§]Median and range. CSICU: Cardiac surgical Intensive Care Unit

transfusion than the matched control raises the concern of how the bleeding was controlled in the control group with less transfusion and without the use of rFVIIa which may lead us to think that the two groups were not well matched.

Payani *et al.*^[20] in a randomized clinical trial studied the effect of prophylactic use of low dose 40 mcg/kg rFVII on patients undergoing redo valve surgeries. They concluded that 40 mcg/kg of rFVII could be effective in reducing the volume of postoperative chest tube drainage and need for blood transfusion, with no thromboembolic event. Overall postoperative ICU stay was not different, while extubation was delayed in the placebo group.

Safari *et al.*^[21] in their analysis of outcomes of a low-dose rFVIIa protocol, they found that chest tube output declined from a mean of 350 to 85 mL/h within 60–90 min of rFVIIa administration. There were no arterial thrombotic events through discharge. Andersen *et al.*^[16]

compared low-dose rFVIIa administration (<60 mcg/kg) to propensity-matched control patients during complex thoracic aortic operations. Their findings suggest that rFVIIa led to fewer postoperative transfusions and no requirement for postoperative rFVIIa administration or re-exploration for bleeding. The safety profile of rFVIIa appeared promising, with few overall adverse events observed in the rFVIIa group and no apparent increase in adverse events compared with control patients.

Romagnoli *et al.* in two reports^[22,23] showed that small dose rFVIIa significantly reduced postoperative bleeding and patients needed less packed red cells, fresh frozen plasma, and platelet transfusion, and they had a reduced re-exploration rate, ICU LOS, and mortality. Two study patients had postoperative stroke, and in the remaining patients, no thromboembolic complication was detected.^[23] Van de Garde *et al.*^[24] found that rFVIIa dose of 40 mcg/kg stopped bleeding in seven patients who had uncontrolled bleeding after cardiac surgery.

On the other hand, the studies which compared low dose to high-dose rFVIIa were scant. Their conclusions are conflicting. Feih *et al.*^[25] found that there were no statistical differences in efficacy or safety between low-dose and high-dose rFVIIa for excessive bleeding following cardiac surgery. However, there were numerically higher rates of redosing with the low-dose group and rates of TEA with the high-dose group.

Alfirevic *et al.*^[26] underwent a dose-response analysis using multivariate logistic regression. He did not find any increase in the risk of mortality between high-dose (>60 mcg/kg) and low-dose (<60 mcg/kg) rFVIIa treatment groups.

Chapman *et al.*^[27] found no clear relationship between adverse outcomes and dose. It was difficult to make any conclusions about rFVIIa dose in this study, but it did seem to suggest that higher doses are not related to increased adverse outcomes.

Masud *et al.*^[28] performed a subgroup analysis on the potential dose effect relationship of each rFVIIa dosing quartile > 30 mcg/kg. He found no significant differences in the magnitude of RBC reduction or percent of patients requiring massive transfusion among the quartiles. No adverse thrombotic episodes were noted, and the observed mortality (22.6%) was not attributed to rFVIIa therapy. However, in that study, analysis was based on the magnitude of transfused RBC reduction, and not on bleeding.

On the other hand, Hacquard *et al.*^[29] found a statistically significant association between the dose and bleeding outcomes. The mean dose infused in the group of patients with bleeding arrest was around 80 mcg/kg, whereas the mean dose infused in the group of patients with sustained bleeding was around 65 mcg/kg. Their data suggest that the most effective dose is at least 80 mcg/kg. This allows only grade E recommendations according to the design of their study.

Gill *et al.*^[14] in a randomized placebo-controlled trial showed that 80 mcg/kg rFVIIa group was superior to 40 mcg/kg rFVIIa group regarding decrease in both reoperations due to bleeding and drainage rate when compared to placebo. Both rFVIIa groups were almost equally superior to placebo regarding the blood transfusion volumes and the proportion of patients avoiding transfusions. Critical serious adverse events were almost the same in the two subgroups of rFVIIa although numerically but not significantly higher in the whole rFVIIa group compared to placebo.

Willi *et al.*^[15] extracted data from the hemostasis registry of The Australian and New Zealand registry that records cases of off-license rFVIIa. Univariate analyses compared patients receiving ≤ 40 , 41–60, 61–80, 81–100, and >100 mcg/kg of rFVIIa. They demonstrated no significant differences in the rate of TAEs, response to bleeding, or 28-day mortality.

Omar *et al.*^[30] conducted a subgroup analysis for a group of patients received rFVIIa for uncontrolled bleeding. He showed that cardiothoracic surgery subgroup had 4.3% thrombotic events. At the multivariate logistic regression model, there were no independent predictors of the occurrence of thrombotic events in patients receiving rFVIIa. Mortality was unrelated to the occurrence of thrombotic events.

The limitations of this study are, first: being a retrospective study; it can only identify associations rather than cause-and-effect relationships and cannot exclude the role of unmeasured confounders in the observed associations. Second: the low-dose rFVIIa used in this study (40–50 mcg/kg) is not the lowest dose used in the literature. It is simply extrapolated from half dose of rFVIIa in hemophiliacs. There was no clear explanation why this particular dose is used and considered as low dose in our institution. Third: while the decision to or not to give rFVIIa for a bleeding patient usually followed a strict protocol, there was no clear objective reason for the choice of high or low dose rather than what we can say an expert opinion of the surgeon and

the intensivist. This can be explained by heterogeneity among the patients; baseline risk, surgical complexity, and condition at the time of rFVIIa therapy (e.g., amount and rate of blood loss, hemodynamic status, and organ compromise). In addition, many cardiac surgeons and intensivists have been involved in this long duration of the study which may have led to variations in their triggers for administration of rFVIIa in addition to choice of the dose. On the other hand, the strength of the study arises from that the patients in our study were treated in a single institution according to standardized clinical guidelines. Moreover, our patient population was more homogeneous than in other published studies.

Conclusion

In this report, low-dose rFVIIa showed equivalent efficacy and safety to high-dose rFVIIa. Further prospective randomized studies are needed to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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