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Recombinant Activated Factor VII (rFVIIa) Treatment of Refractory Bleeding in Cardiac Surgical Patients

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Abstract

Objective: Our aim to evaluate the efficacy and safety of rFVIIa in cardiac surgical patients with refractory bleeding.

Design: The study was a retrospective study.

Setting: Prince Sultan cardiac center, Saudia Arabia.

Participants: Data were collected in patients who had undergone cardiac surgery and complicated by refractory bleeding. The study included 35 patients adults and 8 children.

Interventions: rFVIIa administration.

Measurements and main results: The rFVIIa effect was assessed by the decrease in the chest blood loss (The amount of bleeding was < 3ml/kg/hr without accumulation of blood inside the chest) and number of blood products (Packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate) given before and after rFVIIa administration was recorded. The dose of rFVIIa was 93.72 ± 17.39 µg/kg. All patients received single dose of rFVIIa, but nine patients received a second dose through half to one hour following the initial dose. The blood losses before rFVIIa administration was 7.47 ± 1.53 ml/kg/hr and decreased significantly to 2.37 ± 0.67 and 1.08 ± 0.42 ml/kg/hr in the next six and eighteen hours respectively (P=0.001)[paired test]. Before rFVIIa administration, the number of transfused packed RBC, fresh frozen plasma, platelets and cryoprecipitates were 11.25 ± 3.57, 11.35 ± 4.15, 11.77 ± 4.40 and 10.16 ± 3.76 units and decreased significantly to 5.930 ± 1.704, 3.86 ± 1.52, 3.65 ± 1.42 and 2.91 ± 2.11 units respectively after rFVIIa (P=0.00).

Conclusion: In patients undergoing cardiac surgery exhibiting refractory bleeding, rFVIIa at a mean dose of 93.7 ± 17 µg/kg improved significantly hemostasis and decreased additional administration of blood products, without any complication related to rFVIIa.

Keywords: Cardiac surgery; (rFVIIa); FFP; Platelets; Cryoprecipitates; PRBC; Refractory bleeding; Complications

Introduction

Postoperative bleeding is one of the most common complications following cardiopulmonary bypass (CPB) in patients undergoing cardiothoracic surgical procedures. The reported incidence of clinically refractory bleeding and coagulopathies following cardiac surgery ranges between 4% and 32% [1,2]. Treatment strategies for post-operative bleeding include supportive care with volume resuscitation, the administration of blood products, pharmacologic intervention, and surgical re-exploration [3,4]. Surgical re-exploration is usually complicated by excessive bleeding and has been associated with a three to fourfold increase in mortality, and with superimposed morbidities including renal failure, sepsis, atrial arrhythmias, prolonged mechanical ventilatory support, and increased length of hospital stay [5]. Accordingly, alternative safe and effective strategies to prevent and treat postoperative bleeding are crucial.

Multiple approaches have been proposed to decrease blood loss in this population, with varying degrees of success [6]. Recombinant activated factor VII (rFVIIa) is a clotting factor that can initiate coagulation independent of factors VIII and IX. Coagulation is triggered locally at the site of vascular injury where rFVIIa binds with tissue factor, and activates factors IX and X. The active forms (ie, IXa and Xa) ultimately leading to thrombin generation and clot formation as a result of a stabilized platelets plug and tight fibrin structure resistant to lysis. Given its local effects at the site of vascular injury, rFVIIa may have a role in achieving hemostasis in patients experiencing refractory postoperative bleeding complications [7,8]. It also reverses the effect of warfarin in healthy volunteers [9], and corrects the prothrombin time in patients with hepatic failure [10].

rFVIIa is currently approved for episodes of severe haemorrhage or perioperative management of bleeding in patients with congenital factor VII deficiency and haemophilia A or B with inhibitors [9,11], There subsequently has been an off-label use of rFVIIa for the management of various non-haemophilic bleeding conditions. Such as that due to acquired or congenital thrombocytopathy [12], extensive trauma, and a variety of surgical procedures including anecdotal reports in cardiac surgery patients [13,14]. The aim of our study was to evaluate the efficacy and outcomes of recombinant activated factor VII (rFVIIa) in cardiac surgical patients with intraoperative or postoperative refractory bleeding.

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Material and Methods

The study was an observational study, with data collected in consecutive patients who had undergone cardiac surgery between 2007 and 2009 in the Prince Sultan cardiac center (PSCC), Saudia Arabia. The study included 43 patients [25 males, 18 females, 8 pediatric and 35 adults' patients]. Included patients were those who still had refractory bleeding either intraoperatively (there was excessive generalized oozing and unable to close the chest) or postoperative (if the chest loss more than 3 ml/kg/hr and not responding to conventional treatment). This was defined by persisting bleeding despite accurate surgical hemostasis and exploration at the end of the surgery procedure and a reversal of heparin by protamine guided by ACT. The surgical bleeding source was excluded by surgical re-exploration. In these patients recombinant activated factor VII (rFVIIa, Novoseven; Novo Nordisk, Bagsvaerd, Denmark) was administered when the blood loss amount evoked a significant compromise in systemic hemodynamics despite a standardized blood products transfusion protocol.

Patients were excluded rFVIIa was administered while persistent bleeding source was surgical at surgical re-exploration.

All patients were assessed preoperatively, regarding the coagulation profiles, anticoagulation medication (aspirin, heparin, low molecular weight heparin, plavix and warfarin), renal and liver function. Anaesthetic techniques included a variety of drugs, including etomidate, rocuronium, fentanyl, propofol, and sevoflurane, often in combination. All patients received tranexamic acid (20 mg/kg load, 10 mg/kg/hr infusion for the duration of the procedure). Regarding anticoagulation, all patients received 4mg/kg of heparin before bypass, aiming to provide an activated clotting time of greater than 480 seconds. After bypass, heparin was reversed with protamine which was titrated to achieve an activated clotting time of less than 140 seconds. Cardiopulmonary bypass used centrifugal pumps with 1000 to 1500 mL prime of ringer lactate, in addition to antibiotic, solu-medrol and manitol. Both antegrade and retrograde blood cardiolplegia were used. Cooling was passive to around 34°C or active to 20°C during deep hypothermic arrest. Transfusion of blood products was left to the discretion of the treating physician. Packed red cells were administered to keep hemoglobin above 9 g/dl. Platelets, fresh frozen plasma, and cryoprecipitate were administered in batches of four to six units.

When administered, the effect of rFVIIa was assessed by improvement in hemostasis and decreasing chest loss (amount of bleeding in ml/kg/hr) without accumulation of blood inside the chest usually diagnosed by widening of mediastinum, and numbers of blood products (Packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate) given before and after rFVIIa administration.

Patients monitoring

For all patients, the following variables were closely monitored. The mean arterial pressure (MAP), central venous pressure (CVP), chest X-ray (CXR), Laboratory investigations including , hemoglobin level, activated clotting time (ACT), prothrombin time (PT), international normalized ratio(INR), activated partial thromboplastin time (aPTT) platelet, fibrinogen, were performed in the main laboratory.

Statistical methods

Quantitative data are presented as means ± standard deviation (± SD), while frequencies (number of cases) and percentage were used to describe categorical data. Comparison between pre and post values was done using paired *t* test. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Window

Results

Patients

The mean age for adult patients was 53.31 ± 13.77 year and for pediatric patients was 2.74 ± 2.71 year. The mean body weight for adult patients was 85.09 ± 18.15 kg and pediatric was 12.93 ± 9.35 kg. There were three patients with renal impairment (creatinine>115 mmole/l), two patients had elevated liver enzymes and two patients had sickle cell traits, but coagulation profiles were within normal range. Also, there were two patients with pulmonary edema and five patients with acute myocardial infarction, three of them, were unstable on inotropic support and intra-aortic balloon pump. There was no preoperative coagulopathy (Table 1).

Hemodynamics

Patients were hemodynamically stable by volume resuscitations and inotropic support guided by mean arterial pressure and central venous pressure. The chest X- rays showed no widening of the mediastinum or pleural effusions.

Surgical data of patients

The elective cases included 35 patients (81.40%) and the emergency cases were 8 patients (18.60%). Seven patients had only CABG, fourteen patients had CABG with valvular surgery and three patients had CABG with systemic ventricular remodelization (SVR)., Nine cases had valvular surgery, five of them were a redo cases, two cases had ascending aorta replacement and aortic valve replacement(Bental operation) and eight patients had pediatric surgery (two patients had switch repair, two had titralogy of Fallot repair (TOF), one had atrioventricular septal defect repair (AVSD), one had pulmonary artery repair, one had double outlet right ventricle repair (DORV) and one had Fontan operation (Table 2).

Cardiopulmonary bypass data of patients

All patients were given heparin, the mean dose was 259.23 ± 138.96

Item	Number of patients (total 43)
Age (yr) adult(n=35)	53.31 ± 13.77
Pediatric(n=8)	2.74 ± 2.71
Weight (kg) Adult	85.09 ±18.15
Pediatric	12.93 ± 9.35
Sex n (%) Male	25 (58.13 %)
Female	18 (41.83%)
Ischemic heart	24 (5with AMI)
Hypertension	19(44.18%)
Diabetes mellitus	20(46.51%)
Renal (creatinine >115 mmole/l)	
Impairment	3(6.97 %)
Dialysis	0
Liver (enzymes > 2 folds)	2(4.65 %)
Respiratory (pulmonary edema)	2(4.65 %)
Neurological (carotid stenosis>50%)	5(11.62 %)
Hematological (sickle cell trait)	2(4.65 %)
Euro score(additive) only for adult	10.163 ± 2.775

Values are expressed as number, %, mean(SD)

Table 1: General data of patients.

Cardiac surgery	Number of patients (total 43)
Elective	35(81.40%)
Emergency	8(18.60%)
CABG	7(16.27%)
CABG + Valvular	14(32.54%)
CABG + Valvular+ SVR	3(6.97%)
Valvular	
Single	1(2.32%)
Double or tripple redo cases	5(11.62%)
New cases	3(6.97%)
Bental operation	2(4.65%)
Switch repair	2(4.65%)
TOF	2(4.65%)
AVSD	1(2.32%)
DORV repair	1(2.32%)
Fontan operation	1(2.32%)
Pulmonary artery repair	1(2.32%)

CABG=coronary artery bypass grafting, SVR= systemic ventricular remodelization, TOF=tetralogy of Fallot, AVSD = atrioventricularseptal defect, DORV=double outlet right ventricle. Values are expressed as number, %,

Table 2: Surgical data of patients.

Item	Number of patients (total 43)
Tranexamic acid	all patients (100%)
Heparin dose (mg)	259.23 ± 138.96
Post heparin ACT(seconds)	626.14 ± 131.70
Protamine dose (mg)	267.79 ± 140.30
Post protamine ACT(seconds)	137.79 ± 16.17
CPB time(minutes)	109.39 ± 29.42
CC time(minutes)	88.55 ± 24.65
Temperature(°C)	29.48 ± 2.89

CPB=Cardiopulmonary bypass, CC=Cross clamping, ACT= Activated clotting time Values are expressed %, mean(SD)

Table 3: Intraoperative data of patients.

mg, and the mean activated clotting time was 626.14 ± 131.70 seconds. After weaning from CPB, and stabilization of patients, reversal of heparin with protamine 267.79 ± 140.30 mg was obtained guided by activated clotting time which was 137.79 ± 16.17 seconds. The mean duration of CPB time was 109.39 ± 29.42 minutes, aortic cross clamping time was 88.55 ± 24.65 minutes and the mean temperature during CPB was 29.48 ± 2.89^{o}C (Table 3).

Recombinant Activated Factor VII (rFVIIa) and blood loss

The novoseven (rFVIIa, Novoseven; Novo Nordisk, Bagsvaerd, Denmark) was given intraoperatively after weaning from CPB to six patients due to hemeostsis difficulty and postoperatively within six hours of arriving in the CSICU to 37 patients due to refractory bleeding and increased blood loss through the chest drain. The mean dose was 93.72 ± 17.39 µg/kg (Table 4). All patients received at least one dose of rFVIIa but, nine patients continued to have bleeding after the first dose and received a second dose through 30 minutes to one hour. The mean blood losses before rFVIIa administration was 7.47 ± 1.53 ml/kg/hr and decreased significantly after six hours of receiving rFVIIa to 2.37 ± 0.67 ml/kg/hr (P=0.001) and in the next eighteen hours to 1.08 ± 0.42 ml/kg/hr (P=0.001). The hemoglobin level before rFVIIa administration was 9.66 ± 2.60 g/dl and after rFVIIa and blood transfusion was 10.65 ± 1.73 g/dl with P=0.211 (Table 4).

Blood products transfusion

Before rFVIIa administration, the number of transfused packed

	Before rFVIIa Treatment	After rFVIIa Treatment	P-value
Blood loss (ml/kg/hr)	7.47 ± 1.53		
First 6 hr blood loss (ml/kg/hr)	-	2.37 ± 0.67	0.001
Following 18 hr blood Loss (ml/kg/hr) -	-	1.08 ± 0.42	0.001
P-RBC (units)	11.25 ± 3.57	5.93 ± 1.70	0.001
Platelet (units)	11.77 ± 4.40	3.65 ± 1.42	0.001
FFP (units)	11.35 ± 4.15	3.86 ± 1.52	0.001
Cryoprecipitate (units)	10.16 ± 3.76	2.91 ± 2.11	0.001
PT (seconds)	11.05 ± 1.29	11.32 ± 1.49	0.244
INR	1.21 ± 0.18	1.25 ± 0.22	0.126
aPTT (seconds)	45.53 ± 9.81	41.25 ± 8.82	0.036
ACT(seconds)	138.19 ±16.15	136.60 ± 11.62	0.604
Platelet (x103/dl)	149.74 ± 44.51	154.65 ± 50.67	0.237
Fibrinogen (gm/l)	3.59 ± 0.49	3.94 ± 0.43	0.603
HB (g/dl)	9.66 ± 2.60	10.65 ± 1.73	0.211
rFVIIa Intraoperative (6 patients)			
Postoperative (37 patients)			
Dose (µg/kg) 93.72 ± 17.39			

P-RBC=packed- red blood cells, FFP = fresh frozen plazma, HB= heamoglobin, PT= prothrombin time, INR =international normalized ratio, aPTT =activated prothrombin time, rFVIIa = activated recombinant factor VII. Values are expressed as number, %, mean(SD)

Table 4: Blood loss, blood products transfusion and coagulation profiles before and after rFVIIa.

RBC units, was 11.25 ± 3.57 unit and decreased significantly after giving rFVIIa to 5.930 ± 1.704 unit (P=0.001). Also the number of fresh frozen plasma units before rFVIIa was 11.35 ± 4.15unit and reduced after receiving rFVIIa to 3.86 ± 1.52 unit, (P=0.001). In comparison of platelets given before and after rFVIIa, the number of units was 11.77 ± 4.40 unit, and reduced significantly to 3.65 ± 1.42 unit, with P=0.001. The number of cryoprecipitates received before rFVIIa was 10.16 ± 3.76 unit and reduced significantly after rFVIIa to 2.91 ± 2.11 unit, with P=0.001 (Table 4).

Coagulation profiles

The PT before rFVIIa administration was 11.05 ± 1.29 second and after rFVIIa was 11.32 ± 1.49 second with no significant difference (P=0.497). Also the INR was 1.21 ± 0.18 before and 1.25 ± 0.22 and the P- value was insignificant (P= -0.3180). Before receiving the rFVIIa, the aPTT was 45.53 ± 9.81 and decreased significantly to 41.25 ± 8.82 after receiving the rFVIIa with P=0.036. The ACT level directly before giving the rFVIIa was 138.19 ± 16.165 and decreased to 136.60 ± 11.62 with P=0.604. The platelet number before rFVIIa was 149.74 ± 44.51 and after receiving rFVIIa and platelets transfusion, become 154.651 ± 50.673 with insignificant P=0.237. There was no significant difference between the fibrinogen level before 3.59 ± 0.49 gm/l and after giving rFVIIa 3.94 ± 0.43 gm/l with P=0.603 (Table 4).

Postoperative outcomes

Postoperatively, the complications involved five mortality cases, two cases due to severely unstable heamodynamics (one on the third day and the other on the seventh day), and the other three (from the second to the sixth week) due to prolonged ventilation, severe sepsis and multisystem organs failure [ARDS, renal, liver, myocardium (low cardiac output)]. There were three patients with acute respiratory distress syndrome (ARDS), new two cases with renal impairment (creatinine

complication	Number of patients (total 43)
Acute MI	0
Chronic renal failure	3(6.97%)
Renal impairment	2(4.65%)
Neurological (stroke CT – brain)	1(2.32%)
MOF(ARDS, renal, Liver, myocardium)	3(6.97%)
Infection (wound infection –pneumonia)	4(9.30%)
Mortality(Early)	2 (4.65%)(day 3 - day7)
(Late)	3(6.97%)(week2–week6)
DVT	0
DIC	0
PE	0
LOS (ICU>one month)	2(4.65%)
(hospital I>one month)	1(2.32%)

MI = myocardial infarction, ARDS =acute respiratory distress syndrome, DIC=disseminated intravascular coagulopathy, DVT =deep venous thrombosis; MOF =multisystem organ failure, PE = pulmonary embolism, LOS= length of stay. Values are expressed as number, %.Day 3=the third postoperative day, day 7= the seventh postoperative day, week 6=the sixth postoperative week

Table 5: Postoperative outcomes.

>115 mmol/l), one patient with neurological problems (cerebral stroke diagnosed by brain CT-scan), four patients with infection (wound and pneumonia), and the length of stay (more than one month) in the ICU was two patients and in the hospital was only one patient (Table 5).

Discussion

Hemorrhagic complications after cardiac surgery are an important cause of death and resource utilization [6]. Factors contributing to blood loss and transfusion after cardiac operations include cardiopulmonary bypass (CPB), dilutional coagulopathy from fluid replacement and massive blood product transfusion, haemodilution, dysfunctional platelet (PLT), consumption of clotting factors, deep hypothermia, inflammatory cascade activation, and excessive fibrinolysis due to release of tissue plasminogen activator (tPA) [15-18]. The amount of blood and blood products used during these operations is substantial, and cardiac surgery including rebleeding, now account for approximately 15% of the yearly utilization of the entire banked blood supply in both the US and the UK [19,20]. In addition to issues related to cost and availability of blood and blood products, large volume blood product transfusions are associated with the risk for transfusion related reactions, infectious complications, hypothermia, DIC, excessive fibrinolysis, dilutional coagulopathy, and metabolic acidosis, which may further exacerbate bleeding and morbidity, in addition to increased pulmonary vascular resistance [21,22].

Our study recognizes some limitations in particular the small number of patients, its retrospective type and no matched control

Notwithstanding these limitations, the use of rFVIIa reduced significantly the amount of blood loss through the first postoperative 24 hours and the hemostasis was improved without accumulation inside the chest as guided by frequent chest rays. On the other hand, there was significant reduction of transfusion requirements of packed red blood cells, fresh frozen plasma, platelets and cryoprecipitates (all, P<0.001) without any complication related to rFVIIa.

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 μg/kg, and repeated injections were sometimes necessary as a result of the rFVIIa short plasma elimination half-life [1,23]. One case control study included 40 patients age 9.2 -70.1 years, received a low dose of rFVIIa 18 μg/kg, for refractory bleeding after cardiac surgery. Forty propensity score-based greedy matched controls were compared to the study group. Low dose of rFVIIa significantly reduced the 24-h blood loss: 1610 ml versus 3171 ml in the study and control groups, respectively (P<0.001). Thus, hourly bleeding was 51.1 ml [34.7- 65.4 ml] in patients receiving rFVIIa and 196.2 ml/h [142.1-202.9 ml] in controls (P<0.001). Furthermore, patients receiving rFVIIa showed a lower length of stay in the intensive care unit (P<0.001) and shorter mechanical ventilation time (P<0.001). In addition, the use of rFVIIa was associated with reduction of transfusion requirements of red blood cells, fresh frozen plasma and platelets (all, P<0.001). Finally, treated patients showed improved hemostasis with rapid normalization of coagulation variables (partial thromboplastin time, international normalized ratio, platelet count, P<0.001). In contrast, activated prothrombin time and fibrinogen did not differ between groups (P = ns). No thromboembolic-related event was detected in their cohort [24].

Another study done by Karkouti et al. 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 and 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 [25].

The use of rFVIIa is not without its pitfalls. The primary concern when administering rFVIIa for intractable hemorrhage after extracorporeal circulation is promoting a hypercoagulable state.

In our study, there was one case with cerebral stroke but, we doubted that, it might be related to rFVIIa as this patient had bilateral carotid artery stenosis preoperatively, and we are not sure that the cerebral insult either due to hypoperfusion or embolization from aortic cannulation during CPB.

The respiratory complication (ARDS) may be related the massive blood product transfusions or postoperative infection (pneumonia). The renal impairment may be as a result of hypoperfusion or inflammatory process during CPB.

Regarding the thrombo-embolism, there were no clinical manifestations of deep vein thrombosis or embolization, and prophylactic anticoagulants were used early, especially bed-ridden patients who intubated for longer duration and in addition, the Doppler was not a routine for postoperative patients.

There were five mortality cases not related to bleeding or using of rFVIIa, two cases of them due to low-cardiac output not responding to management. The patients were unstable due to preoperative massive acute myocardial infarctions, on much inotropic supports and IABP. Postoperatively, these patients continued to be unstable in spite of the inotropic support and IABP. The other three cases died due to severe sepsis multisystem organ failure.

Nevertheless, despite the use of rFVIIa in 304 cardiac surgery patients with refractory hemorrhage, the incidence of this serious adverse event (thrombotic complications) remains very low (4.6%) [26]. This can be theoretically explained by the presence of potential protective

mechanism which work against thrombotic complications in these patients, the plasma concentration of tissue factor pathway inhibitor (TFPI), a strong inhibitor of the enzymatic activity of the TF — FVIIa complex, rises and remains at a higher levels at the end of CPB [27], However, even though published data have shown a good level of safety in cardiac surgery patients, these subjects must be considered at high risk for thrombotic complications [28]. 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. Another study involved forty cardiac surgical patients, 20 (50%) underwent isolated or combined CABG and they did not show either clinical, or electrocardiographic and echocardiographic signs of graft occlusion. Two study patients had postoperative stroke and in both a predisposing factor was clearly identified; in the remaining patients no thromboembolic complication was detected [29]. In our study, there was new one postoperative case with acute myocardial infarction after giving rFVIIa, in patient post CABG diagnosed early by elevated ST segment and elevated cardiac enzymes with positive tropinin test, after transfering to ICU. The myocardial infarction may be related to inadequate myocardial protection (some patients had severe left ventricular hypertrophy due to aortic valve stenosis) or embolization of air during CPB. Coronary angiography was not done postoperatively, to check the patency of coronary grafts.

Thrombotic adverse events have been reported in 17 hemophilia patients who received rFVIIa between 1996 and 2001. It has been postulated [30,31], that bleeding after cardiac surgery induces disseminated intravascular coagulation and the activation of the hemostatic system with rFVIIa in this setting may increase the risk of thromboembolic events. A study was done by Lucey MA and colleagues involving 20 patients who received rFVIIa following extracorporeal circulation. Two patients (10%) experienced thromboembolic events, and such an event was suspected in a third patient. Both patients have got developed thromboembolic events following lung transplantation. One patient was believed to have experienced massive intracardiac and extracorporeal membrane oxygenation circuit thromboses following the administration of both rFVIIa and activated prothrombin complex concentrate, this patient developed cardiac arrest and died. The other patient developed cardiac tamponade requiring surgical intervention to evacuate a large mediastinal thrombosis following rFVIIa administration. In the third patient, cardiac enzyme levels were elevated on postoperative day 1, and coronary thrombosis was diagnosed [32].

Another study was done by Levi M and colleagues, by giving an initial dose of rFVIIa of about 90 μg/kg. Three patients received a second dose within 30 min because of inadequate clinical response. Response to administration was varied, some patients had a dramatic improvement in hemo¬stasis; some patients had a moderate improvement that allowed for surgical closure to proceed both with and without additional coagulation factors. In some patients the resolution of coagulopathic bleed¬ing revealed previously unidentified surgical bleeding. Four patients (7%) were considered non-responders clinically [33]. This is similar to other reported series. A possible explanation for failure to respond to rFVIIa includes unrecognized surgical bleeding [34].

A study was done by Stefano Romagnoli et al. [35]; 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 increased in the study group (P=0.003). Finally, platelet count was significantly higher in patients treated with rFVIIa (P=0.034), whereas aPTT and fibrinogen did not differ between groups (not significant). Among 15 treated patients, 2 underwent CABG and they showed no clinical, electrocardio-graphic, 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 trans-esophageal echocardiography [35].

Diprose and colleagues reported a randomized, controlled trial (RCT) with 20 patients (9 received rFVIIa) in which a single dose of rFVIIa was used prophylactically at the termination of cardiopulmonary bypass in noncoronary cardiovascular surgery. Although the need for allogeneic blood transfusion was significantly reduced after the administration of rFVIIa, there was no effect on patient survival [36]. Gill et al. reported a placebo-controlled RCT in which patients with bleeding episodes after cardiovascular surgery were randomly assigned to receive a single dose of rFVIIa at 40 mcg/kg (n=35) or 80 mcg/kg (n=69) versus placebo (n=68). Significant decreases in the need for reoperation and allogeneic blood transfusions were seen in the groups that received rFVIIa, but there were no differences in mortality. Furthermore, there were increases in thromboembolic adverse events, particularly stroke, in the rFVIIa groups, although they did not reach statistical significance [37].

In a recent study by Levi and coworkers confirmed an increase in arterial thrombotic adverse events among all published RCTs investigating off-label use of rFVIIa [38]. Previous analyses of voluntary reports to the FDA Adverse Event Reporting System identified deep venous thrombosis, ischemic cerebrovascular accident, and myocardial infarction as the most common adverse events associated with rFVIIa use [39].

Conclusion

We concluded that, the Recombinant Activated Factor VII (rFVIIa) improved significantly hemostasis and decreased refractory blood loss either intraoperatively or postoperatively in patients undergoing cardiac surgery, in addition to the decreased requirement to the blood products, without any complication related to rFVIIa.

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