Original Article

Impact on postoperative bleeding and cost of recombinant activated factor VII in patients undergoing heart transplantation

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ABSTRACT

Background: Cardiac transplantation can be complicated by refractory hemorrhage particularly in cases where explantation of a ventricular assist device is necessary. Recombinant activated factor VII (rFVIIa) has been used to treat refractory bleeding in cardiac surgery patients, but little information is available on its efficacy or cost in heart transplant patients. **Methods:** Patients who had orthotopic heart transplantation between January 2009 and December 2014 at a single center were reviewed. Postoperative bleeding and the total costs of hemostatic therapies were compared between patients who received rFVIIa and those who did not. Propensity scores were created and used to control for the likelihood of receiving rFVIIa in order to reduce bias in our risk estimates. **Results:** Seventy-six patients underwent heart transplantation during the study period. Twenty-one patients (27.6%) received rFVIIa for refractory intraoperative bleeding. There was no difference in postoperative red blood cell transfusion, chest tube output, or surgical re-exploration between patients who received rFVIIa and those who did not, even after adjusting with the propensity score (P = 0.94, P = 0.60, and P = 0.10, respectively). The total cost for hemostatic therapies was significantly higher in the rFVIIa group (median $10,819 vs. $1,985; P < 0.0001). Subgroup analysis of patients who underwent redo-sternotomy with left ventricular assist device explantation did not show any benefit for rFVIIa either. **Conclusions:** In this relatively small cohort, rFVIIa use was not associated with decreased postoperative bleeding in patients undergoing heart transplantation; however, it led to significantly higher cost.

Received: 21-03-16
Accepted: 25-05-16

Key words: Bleeding; Heart transplantation; Recombinant activated factor VII; Transfusion

INTRODUCTION

Cardiac transplantation can be a complex surgical procedure, particularly in patients requiring redo-sternotomy and left ventricular assist device (LVAD) explantation. Some patients have excessive blood loss and require transfusion of multiple blood products and surgical re-exploration.[1] About 5–7% of patients lose 2 L of blood within the first 24 h after surgery, and up to 5% require subsequent trips to the operating room for bleeding.[2] Blood transfusion and surgical re-exploration are both associated with prolonged Intensive Care Unit stay, hospital stay, and reduced survival.[3]

Recombinant activated factor VII (rFVIIa) is an Food and Drug Administration approved

Access this article online
Website: www.annals.in
DOI: 10.4103/0971-9784.185523
Quick Response Code:

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Cite this article as: Hollis AL, Lowery AV, Pajoumand M, Pham SM, Slejko JF, Tanaka KA, *et al*. Impact on postoperative bleeding and cost of recombinant activated factor VII in patients undergoing heart transplantation. Ann Card Anaesth 2016;19:418-24.

drug for treating refractory bleeding in patients with hemophilia A or B who have antibody inhibitors to factor VIII or IX. It has also been used off-label to treat severe hemorrhage in cardiac surgery and trauma.[4-8] rFVIIa has been used in cardiac transplantation to treat refractory bleeding. One small observational study of 17 patients suggested that it decreased postoperative bleeding, but was associated with a high rate of thromboembolism.[9] rFVIIa also has substantial cost, and there are persistent concerns about its safety.[6]

The purpose of this study was to determine whether rFVIIa use was associated with decreased postoperative bleeding in patients undergoing heart transplantation and whether it was associated with increased cost. We hypothesized that rFVIIa administration would not be associated with decreased bleeding, but would increase costs.

METHODS

Subjects

The Institutional Review Board at the University of Maryland, Baltimore, approved the study. A retrospective cohort study was performed which included all adult patients who had cardiac transplantation at the University of Maryland Medical Center between January 1, 2009 and December 31, 2014. The investigators identified patients for inclusion in the study using the Institutional Society for Thoracic Surgeons database, which contains data on all patients having cardiac surgery at our center.

Study data

For all subjects, the following demographic data, medical comorbidities, and preoperative laboratory values were collected using electronic medical records and scanned hospital documents: Age, sex, body weight, preoperative diagnosis, history of previous cardiac surgery, history of LVAD insertion, preoperative platelet count, preoperative hemoglobin concentration, and preoperative International Normalized Ratio (INR).

We also collected the following intraoperative variables: Cardiopulmonary bypass time, red blood cell (RBC) transfusion, fresh frozen plasma (FFP) transfusion, platelet transfusion, cryoprecipitate transfusion, and rFVIIa administration. Finally, we collected the following postoperative data: 24 h chest tube output, 24 h RBC transfusion, first postoperative hemoglobin, first postoperative platelet count, first postoperative INR, thrombosis (venous or arterial), reoperation for bleeding, and in-hospital death. All transplants were performed by one of the three transplant surgeons at our center.

Transfusion practices

Attending anesthesiologists, cardiac surgeons, and intensivists made all transfusion decisions during the study period. General transfusion thresholds for bleeding patients at our center are RBC transfusion for a hemoglobin level <7 mg/dL, FFP transfusion for an INR >1.5, platelet transfusion for a platelet count <100,000 platelets/μL, and cryoprecipitate transfusion for a fibrinogen level <200 mg/dL. Our standard antifibrinolytic is epsilon aminocaproic acid, which is given as a 10 g bolus and infused as 1 g/h during surgery and until approximately 6 h after. All patients in the study received an antifibrinolytic. There was no specific algorithm for rFVIIa use at our center during the study period. rFVIIa was given at the discretion of attending anesthesiologists and cardiac surgeons depending upon the perceived degree of coagulopathy.

Outcome variables

The primary study outcome variable was 24 h chest tube output after surgery. The secondary study outcomes were 24 h RBC transfusion and reoperation for bleeding.

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Distributions for variables were examined using histograms for continuous variables and two by two tables for categorical variables. Continuous variables were summarized as the median and interquartile range (Q1, Q3), and categorical variables were summarized as number and percentage of the cohort. Continuous variables were compared between patients who received rFVIIa and those who did not using the Wilcoxon rank sum test. Categorical baseline variables were compared between patients who received rFVIIa and those who did not using the Chi-square test.

Outcome variables that were continuous were compared between those who received rFVIIa and those who did not using the Wilcoxon rank sum test. Outcome variables that were dichotomous categorical variables were compared between patients who received rFVIIa and those who did not use the Chi-square test.

The impact of rFVIIa on the outcome variables of interest was modeled using three different regression

models. Specifically, the relationship between rFVIIa administration and postoperative chest tube output was modeled using linear regression. A crude risk difference with a 95% confidence interval (CI) was calculated for postoperative chest tube output between those who received rFVIIa and those who did not. The relationship between rFVIIa administration and 24 h postoperative RBC transfusion was modeled using Poisson regression. A crude rate ratio with a 95% CI was calculated for the number of RBC units transfused in those who received rFVIIa compared to those who did not. Finally, a crude odds ratio (OR) with a 95% CI was calculated for the odds of undergoing a reoperation for bleeding in patients who received rFVIIa.

Propensity score analysis

To control for important confounders, we created a propensity score for each patient that represented the likelihood of receiving rFVIIa during surgery. The propensity score was created using logistic regression with the following variables entered as independent variables in the model: Age, sex, diagnosis, previous sternotomy, LVAD prior to surgery, preoperative platelet count, preoperative hemoglobin, preoperative INR, intraoperative RBC transfusion, intraoperative FFP transfusion, intraoperative cryoprecipitate transfusion, and receipt of rFVIIa as the dependent variable. The propensity score was then included along with rFVIIa as the exposure variable to calculate an adjusted difference in chest tube output (linear regression), an adjusted rate ratio for RBC transfusion (Poisson regression), and an adjusted OR for reoperation (logistic regression). 95% CI were calculated for all adjusted risk estimates.

Subgroup analysis

A decision was made *a priori* to also perform a subgroup analysis, which included only patients who had redo-sternotomy with LVAD explantation. For this subgroup analysis, we compared continuous outcome variables using the Wilcoxon rank sum test and categorical outcomes using the Chi-square test.

Cost analysis

Costs of hemostatic therapies were compared for those who received rFVIIa and those who did not. Cost estimates (adjusted for 2015 USD) were provided by the blood bank at our institution for common hemostatic therapies and were as follows: 1 unit of apheresis platelets = $505, 1 unit of FFP = $53, 1 pool of cryoprecipitate = $380, and 1 mcg of rFVIIa = $1.52. The total cost for all intraoperative hemostatic therapies was calculated for each patient in the cohort. Costs of intraoperative hemostatic therapies were then compared between patients who received rFVIIa and patients who did not using the Wilcoxon rank sum test.

RESULTS

Patient characteristics

During the study period, 76 patients underwent orthotopic heart transplantation at our center. 21 patients (27.6%) were treated with rFVIIa. Patient demographics and characteristics are summarized in Table 1. Patients who received rFVIIa had a higher risk profile than those who did not. They had a lower preoperative hemoglobin, longer cardiopulmonary bypass time, and required substantially more blood products in the operating room. Thirty patients had an LVAD prior to heart transplantation; 10 of them (47.6%) received rFVIIa in the operating room.

Effect on postoperative bleeding

There was no difference in unadjusted 24 h chest tube output or RBC transfusions between patients who received rFVIIa and those who did not [Table 2]. Patients who received rFVIIa had a median 24 h chest tube output of 1365 mL, whereas those who did not receive rFVIIa had a median output of 1150 mL. Patients who did not receive rFVIIa required more RBC transfusions postoperatively, but this difference was not statistically significant (2 units vs. 1 unit, $P = 0.59$). After correcting for the likelihood of receiving rFVIIa with the propensity score, there was no difference in adjusted chest tube output or postoperative RBC transfusion [Table 3].

Effect on reoperation for bleeding

Patients who received rFVIIa were more likely to return to the operating room for bleeding, (42.9% vs. 20.0%, $P = 0.04$). However, after correcting for the likelihood of receiving rFVIIa with the propensity score, there was no difference in the rate of reoperation for bleeding; OR = 3.24 (95% CI = 0.78–13.49), $P = 0.10$.

Thrombosis

The rate of postoperative thromboembolic events did not differ after stratification by rFVIIa use. Patients receiving rFVIIa had a 33.3% rate of thromboembolism compared to a rate of 32.7% in patients who did not receive rFVIIa ($P = 0.96$).

Recombinant activated factor VII dose

The median total dose of rFVIIa was 4.5 mg (total dose range = 2–10 mg or 24–111 mcg/kg). Four patients

Table 1: Patient characteristics

Variable	Full cohort *n*=76	VIIa patients *n*=21	Non-VIIa patients *n*=55	*P* value
Age	60 (49, 66)	57 (49, 64)	60 (49, 67)	0.93
Sex (% male)	62 (81.6)	19 (90.5)	43 (78.2)	0.21
Weight (kg)	83 (69, 96)	83 (69, 94)	82 (68, 96)	0.97
Diagnosis				
NICM	41 (54.0)	10 (47.6)	31 (56.4)	0.06
ICM	27 (35.5)	6 (28.6)	21 (38.2)	
Other	8 (10.5)	5 (23.8)	3 (5.5)	
Previous sternotomy	40 (52.6)	13 (61.9)	27 (49.1)	0.32
LVAD prior to transplant	30 (39.5)	10 (47.6)	20 (36.4)	0.36
Preoperative Platelet count (x 10^3/uL)	186 (149, 225)	177 (142, 221)	190 (152, 225)	0.79
Preoperative Hemoglobin (g/dl)	11.1 (9.9, 12.4)	10.3 (9.2, 10.9)	11.7 (10.1, 13.2)	0.005
Preoperative INR	1.7 (1.3, 2.1)	1.8 (1.4, 2.3)	1.6 (1.2, 2.0)	0.10
CPB time (minutes)	181 (133, 224)	209 (165, 241)	163 (127, 204)	0.04
Intraoperative RBC units	7 (3, 10)	10 (8, 14))	4 (2, 9)	0.0003
Intraoperative Platelet units	3 (2, 4)	3 (3, 4)	2 (2, 3)	0.005
Intraoperative FFP units	8 (6, 12)	13 (9, 17))	7 (5, 10	0.001
Intraoperative Cryoprecipitate volume (mL)	20 (0, 220)	220 (12, 224)	0 (0, 120)	0.03

Data are median (Q1, Q3) or *n* (%). FFP: Fresh frozen plasma, ICM=Ischemic cardiomyopathy, INR: International normalized ratio, LVAD: Left ventricular assist device, NICM: Non-ischemic cardiomyopathy, RBC: Red blood cell

Table 2: Outcomes for cohort

Variable	Full Cohort *n*=76	VIIa patients *n*=21	Non-VIIa patients *n*=55	*P* value
ICU 24 hour chest tube output (mL)	1220 (785, 1970)	1365 (875, 3170)	1150 (730, 1845)	0.25
ICU 24 hour RBC transfusion (units)	2 (0, 4)	1 (0, 7)	2 (0, 4)	0.59
First post-operative hemoglobin in ICU (g/dL)	9.8 (9.0, 10.5)	9.4 (8.9, 10.5)	9.8 (9.1, 10.5)	0.45
First post-operative INR in ICU	1.5 (1.3, 1.7)	1.2 (1.0, 1.5)	1.6 (1.4, 1.8)	0.0002
First post-operative platelet count in ICU (x 10^3/uL)	116 (85, 139)	107 (82, 131)	118 (90, 149)	0.17
Thrombosis	25 (32.9)	7 (33.3)	18 (32.7)	0.96
Reoperation for bleeding	20 (26.3)	9 (42.9)	11 (20.0)	0.04
Operating room cost for all hemostatic products (USD$)	2812 (1355, 7527)	10819 (8809, 11793)	1985 (1222, 3401)	<0.0001

Data are median (Q1, Q3) or *n* (%). INR: International normalized ratio, RBC: Red blood cell

received multiple doses of rFVIIa. One of these patients received 2 separate doses of 5 mg, which was the highest total dose of all patients. This patient had a redo-sternotomy due to rejection of a prior allograft and was massively transfused in the operating room. A second patient received three 2 mg doses of rFVIIa. This patient had a redo-sternotomy with LVAD explantation.

Subgroup analysis of patients with left ventricular assist device explantation

Table 4 shows the subgroup analysis of patients who underwent LVAD explantation. There was no difference in 24 h chest tube output, postoperative RBC transfusion, postoperative hemoglobin level, or reoperation for bleeding between patients who received rFVIIa and patients who did not. Patients who received rFVIIa had a significantly lower postoperative INR (1.1 vs. 1.6, $P = 0.001$).

Cost analysis

Costs of hemostatic therapies were greater for patients who received rFVIIa. The median cost for hemostatic therapies in the rFVIIa group was $10,819 compared to $1985 in patients who did not receive rFVIIa ($P < 0.0001$). In patients who required LVAD explantation, the cost of hemostatic therapies in the operating room was generally higher, but the rFVIIa group had the highest cost. The median cost for hemostatic therapies in the rFVIIa group was $11,755 compared to $2861 in the group who did not receive rFVIIa ($P < 0.0001$).

DISCUSSION

Our study represents the largest observational cohort of cardiac transplant patients receiving rFVIIa to date. Although our study is observational, rFVIIa did not appear to decrease postoperative bleeding or reoperations for bleeding. In addition, it increased the costs of hemostatic therapy by approximately 5-fold.

In a previous retrospective cohort study, Gandhi *et al*. examined the use of rFVIIa in cardiac transplantation. In this study, 9 of 17 patients required LVAD explantation. The author's conclusion was that rFVIIa helped to achieve adequate hemostasis in most cases of refractory bleeding.[9] The postoperative rate of thromboembolism was 29.4% for the cohort. Our study, which has a larger number of patients with LVAD explantation, found no difference in postoperative bleeding after stratification by rFVIIa use. The Gandhi study is limited by the fact that there was no control group. Individual patients were assessed for bleeding in a nonblinded fashion before and after rFVIIa administration, and this could have led to a high level of observer bias.

The current Society of Thoracic Surgery guidelines for bleeding management and transfusion recommend that rFVIIa be used in cardiac surgery patients with refractory microvascular bleeding. However, there is minimal guidance on when rFVIIa should be administered and what dose is appropriate. There is also no recommendation for use based upon the surgery type. In heart transplant patients, there is minimal published data and these patients may be at particularly high risk for thromboembolic complications based on Gandhi's data and our own.

In the Gandhi study, the mean dose of rFVIIa was approximately 80 μg/kg. In the largest randomized controlled clinical trial of rFVIIa use in cardiac surgery patients, Gill *et al*. studied rFVIIa in cases with refractory bleeding. Patients were randomized to placebo, 40 μg/kg, or 80 μg/kg of rFVIIa.[10] There was no statistically significant difference in reoperation for bleeding or blood transfusion in patients who received a dose of 40 μg/kg when compared to patients who received 80 μg/kg of rFVIIa. However, both rFVIIa groups had less bleeding and fewer reoperations when compared to the placebo group. These data do not provide clarity on optimal dosing, but suggested that a 40 μg/kg dose may be adequate. In another observational study by Romagnoli *et al*., a rFVIIa dose as low as 1.2 mg was suggested to have efficacy for refractory bleeding.[11] In this study, low dose rFVIIa administration was associated with decreased transfusion, reduced the Intensive Care Unit length of stay, and fewer surgical re-explorations when subjects were compared against a matched cohort.[11]

A major concern with rFVIIa use is that it has been associated with serious thromboembolic events.[12,13] In our study, a large percentage of patients were found to have a deep venous thrombosis (DVT) after

Table 3: Unadjusted and adjusted risk estimates for the effects of rF VIIa on outcome variables

Patients who received VIIa		
24 hour chest tube model	**Difference in chest tube output (ml) (24 hours post op)**	***P* value**
Crude analysis	410.11 (−621.27, 1441.49)	0.43
Propensity score adjusted	348.95 (−988.20, 1686.10)	0.60
24 hour RBC model	**RBC transfusion rate ratio (24 hours post op)**	
Crude analysis	1.40 (1.09, 1.82)	0.008
Propensity score adjusted	0.99 (0.70, 1.38)	0.94
Reoperation for bleeding model	**Odds ratio for takeback**	
Crude analysis	3.00 (1.01, 8.90)	0.05
Propensity score adjusted	3.24 (0.78, 13.49)	0.10

RBC: Red blood cell

Table 4: Subgroup analysis of patients with LVAD prior to transplantation

Variable	VIIa patients (10)	Non-VIIa patients (20)	*P* value
ICU 24 hour chest tube output (mL)	910 (682, 1380)	1320 (924, 1835)	0.29
ICU 24 hour RBC transfusion (units)	1 (0, 7)	2 (0, 3)	0.82
First post-operative hemoglobin in ICU (g/dL)	9.3 (8.6, 10.0)	10 (9.3, 10.7)	0.15
First post-operative INR in ICU	1.1 (1.0, 1.2)	1.6 (1.5, 1.8)	0.001
First post-operative platelet count in ICU (x10^3/uL)	119 (107, 131)	118 (79, 143)	0.95
Thrombosis	3 (30.0%)	18 (50.0%)	0.29
Reoperation for bleeding	4 (40.0%)	5 (25.0%)	0.39
Operating room cost for all hemostatic products (USD$)	11755 (8809, 13807)	2861 (1912, 3603)	<0.0001

Data are median (Q1, Q3) or *n* (%). INR: International normalized ratio, RBC: Red blood cell

surgery (mostly internal jugular), but there was no statistically significant difference after stratification by rFVIIa use. Most DVTs were presumed to be central line associated, although this is difficult to determine in a retrospective study. Although we did not observe increased thromboembolic events related to rFVIIa, the limited literature from randomized controlled trials using rFVIIa suggests a trend toward increased thromboembolic events.[5,10,14-17]

At the time of our analysis, rFVIIa cost $1.52 per mcg at our center. Patients in our study received between 2 and 10 mg of rFVIIa resulting in high total costs for this medication. In both the full cohort and LVAD subgroup, there was a statistically significant increase in cost when rFVIIa was administered. In fact, rFVIIa increased total costs for hemostatic therapies about 5-fold. Given that we found no beneficial effect on postoperative bleeding, this is a major concern given the continuously rising costs of healthcare.

The majority of patients who had LVAD explantation in our cohort were on warfarin prior to surgery. Goldstein *et al*. evaluated four-factor prothrombin complex (4F-PCC) for rapid Vitamin K reversal in surgical patients. In this study, patients who had a baseline INR between 2 and 4 were given 4F-PCC at a dose of 25 international unit (IU) factor IX per kg and patients with a baseline INR between 4 and 6 were given 50 IU factor IX per kg.[18] Using this algorithm, 34% of the patients in our study could have received 4F-PCC because of an INR >2. At the time of our analysis, 4F-PCC cost $1.91 per IU at our center and this would have led to potentially less cost than rFVIIa administration. Patients would have received a dose of 4F-PCC between 1400 and 3400 IU resulting in a cost between $2674 and $6494. To the best of our knowledge, there are no studies comparing the efficacy of 4F-PCC and rFVIIa in patients who present for surgery with an elevated INR.

Despite there being no observed benefit in terms of postoperative bleeding, patients who received rFVIIa did have lower postoperative INRs our study. This is not surprising as FVII is part of the extrinsic pathway and rFVIIa administration commonly leads to a decrease in INR after administration. This decrease in INR; however, may be a laboratory *(in vitro)* phenomenon that does not translate into decreased postoperative bleeding. The INR is a plasma-based assay that does not account for platelet function, fibrinolysis, and other aspects of coagulation.

Our study has a number of important limitations. First, it is a retrospective observational study with a relatively small sample size. Therefore, it may be underpowered for detecting small differences in postoperative chest tube output or RBC transfusion. Moreover, patients treated with rFVIIa had a markedly higher risk profile and more significant intraoperative bleeding as reflected by higher intraoperative RBC transfusion (median of 10 units compared to 4 units) for the rFVIIa group. In order to control for this imbalance between groups, we used propensity scores; however, propensity scores can only reduce bias when they are calibrated correctly and in small cohorts they may not be able to achieve balance in all important covariates between groups. Finally, our institution had no specific algorithm for rFVIIa administration during the study period. This led to the use of rFVIIa in a variety of circumstances and probably in some patients who did not require it.

CONCLUSIONS

In an observational cohort study of heart transplant patients who were treated with rFVIIa during surgery, there was no observed benefit in terms of postoperative bleeding even after adjusting for the likelihood of receiving rFVIIa. rFVIIa was, however, associated with a 5-fold increase in the cost of hemostatic therapies. Given its high cost and persistent concerns about its safety, rFVIIa use should be reserved for the most refractory bleeding cases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Marietta M, Facchini L, Pedrazzi P, Busani S, Torelli G. Pathophysiology of bleeding in surgery. Transplant Proc 2006;38:812-4.
2. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med 2007;356:2301-11.
3. Hein OV, Birnbaum J, Wernecke KD, Konertz W, Jain U, Spies C. Three-year survival after four major post-cardiac operative complications. Crit Care Med 2006;34:2729-37.
4. Herbertson M. Recombinant activated factor VII in cardiac surgery. Blood Coagul Fibrinolysis 2004;15 Suppl 1:S31-2.
5. 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.
6. Levy JH. Pharmacologic preservation of the hemostatic system during cardiac surgery. Ann Thorac Surg 2001;72:S1814-20.
7. Grounds M. Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: A review. Blood Rev 2003;17 Suppl 1:S11-21.
8. DiDomenico RJ, Massad MG, Kpodonu J, Navarro RA, Geha AS. Use of recombinant activated factor VII for bleeding following operations requiring cardiopulmonary bypass. Chest 2005;127:1828-35.
9. Gandhi MJ, Pierce RA, Zhang L, Moon MR, Despotis GJ, Moazami N. Use of activated recombinant factor VII for severe coagulopathy post ventricular assist device or orthotopic heart transplant. J Cardiothorac Surg 2007;2:32.
10. 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.
11. 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.
12. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295:293-8.
13. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005;352:777-85.
14. Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev 2011;2: CD005011.
15. Ekert H, Brizard C, Eyers R, Cochrane A, Henning R. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: A randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. Blood Coagul Fibrinolysis 2006;17:389-95.
16. Essam M. Prophylactic administration of recombinant activated factor VII in coronary revascularization surgery. Internet J Anesth 2007;13:10.
17. Ma B, Wang Z, Zhang BR, Li J. Effect of recombinant activated factor VIIa on early recovery of patient undergoing cardiac valve replacement under cardiopulmonary bypass; a randomized double-blind placebo-controlled trial. Acad J Second Mil Med Univ 2006;27:1110-3.
18. Goldstein JN, Refaai MA, Milling TJ Jr., Lewis B, Goldberg-Alberts R, Hug BA, *et al.* Four-factor prothrombin complex concentrate versus plasma for rapid Vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: A phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015;385:2077-87.