Timing of Recombinant Factor VIIa Administration for Severe Bleeding in Cardiac Surgery: Does It Make Any Differences?

Abdalla M[1], Ewila H[1,2]*, Eissa M[1], AL Khulaifi A[1] and Singh R[3]

[1]Department of Cardiothoracic Surgery, Heart Hospital, Hamad Medical Corporation, Doha, Qatar.

[2]Department of Anesthesia, Suez Canal University, Ismailia, Egypt.

[3]C.C.S Department, Heart Hospital, Hamad Medical Corporation, Doha, Qatar.

***Correspondence:**
Hesham Ahmed Ewila, Department of Cardiothoracic Surgery/Cardiac Anesthesia & ICU Section, Heart Hospital, Hamad Medical Corporation, Doha, (PO: 3050), Qatar, Tel: 0097466291759.

Received: 05 October 2019; **Accepted:** 30 October 2019

ABSTRACT

Introduction: Perioperative severe bleeding remains a frequent complication in cardiac surgery with high incidence of morbidity and mortality. Recombinant activated factor VII (rVIIa) is administered for the management of many cases of severe bleeding in cardiac surgery with improvement of outcome. We hypothesize that there may be differences in the efficacy and safety of early versus late administration of rVIIa.

Methods: A retrospective descriptive analytic study involved all patients who received rFVIIa in cardiac surgery department over 6 year's duration with a total number of 50 patients. The studied population was divided into two groups according to timing of rFVIIa administration, early group who received rVIIa within the first 2 hours of onset of bleeding (23 patients) and late group if rVIIa was given after 2hours of onset of bleeding (27 patients). Preoperative, intraoperative and postoperative data were collected and statistically analyzed.

Results: There were no significant statistical demographic or surgical differences between the identified groups. Postoperatively we noted statistically significant lower postoperative blood loss (p =.001), blood transfusion (p=.02), Fresh frozen plasma P (p= .02), platelets transfusion (p= .02) and incidence of re-exploration (p=.02) in the early rVIIa administration group. There was no difference in the lengths of mechanical ventilation or hospital stay but length of ICU stay was significantly longer in the late rVIIa administration group.

Conclusion: In this analysis, Early administration of rFVIIa in the management of severe bleeding following cardiac surgery was associated with decreased blood loss, decreased the need for blood and blood products transfusion and decreased Incidence of Re-exploration. Long-term safety remains unclear.

Keywords
Cardiac Surgery, Postoperative bleeding, Recombinant factor VIIa.

Introduction
Perioperative severe bleeding remains major cause of morbidity and mortality in cardiac surgery [1], with relatively high incidence 10%-15% [2]. Many factors are responsible for the complex hemostatic defects including hypothermia, hemodilution, and activation of the coagulation, fibrinolytic, and inflammatory pathways [3,4]. Recombinant activated factor seven (rFVIIa) was administered for management of many cases of severe bleeding in cardiac surgery when conventional therapy has failed with reported improvement of outcome [5-8]. Most of rFVIIa administrations (95%) were off-label as FDA approval for rFVIIa was only for hemophilic patients [9]. Recombinant FVIIa is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton) and structurally similar to human plasma-derived Factor VIIa [10]. Recombinant FVIIa acts by increasing the activity of extrinsic tissue factor [11], also rFVIIa binds to the surface of activated platelets promoting factor X activation and thrombin generation [12].

Decision of rFVIIa administration in our institute is variable in timing of administration or even excluding rFVIIa use. The

dynamicity and multiple factors affecting coagulation makes some physicians delay or hesitate to give rFVIIa in addition to possible thromboembolic complications and off-label state [13]. The hypothesis of this research was to find out if there is difference in the efficacy and safety of early versus late administration of rFVIIa.

Methods

Our study was a retrospective, descriptive, single-center study with purposive sampling that examined the effect of rFVIIa administration timing differences in management of severe bleeding in cardiac surgery. Approval for the study was obtained from the Hamad Medical Corporation ethical committee (reference number MRC 0198 /2017). After institutional research ethics board approval was obtained, Patients were identified from hospital administrative databases from September 2011TO December 2017. We collected detailed perioperative, operative and postoperative data (including demographics, laboratory tests, blood product transfusions, dose and time of rFVII administration, postoperative drainage, re-exploration rates, and postoperative complications).

Fifty patients were recruited in our sample as their cardiac surgery was complicated with severe bleeding and they got administered rFVIIa during the management course. They were subsequently classified into two groups according to the timing of administration of rFVIIa.

Early administration group: 27 patients were identified as they had administered rFVIIa within two hours from the onset of bleeding management course.

Late administration group: It included 23 patients who had administered rFVIIa after 2 hours from the onset of bleeding management course.

Data were retrieved using Cerner Data System hospital Cerner System, (Cerner Corporation, Kansas City, MO, USA) and Dendrite Clinical Systems (London, UK).

Statistical analysis

Descriptive statistics in terms of mean and standard deviation as well as median (inter quartile range) for interval variables and frequency with percentage for categorical variable were performed. Student t tests for normal distributed interval variables and Mann Whitney U tests for non-normal variables were used to see significant mean difference between early admission and late admission group. Chi-square tests were applied for categorical variables to see association between the two groups. Graphical presentation was made for important variables according to two groups. P value 0.05 (two tailed) was considered for the statistically significant level. SPSS22.0 statistical package was used for the analysis.

Results

On comparing data between two groups we found no statistical

differences regarding demographic characteristics, preoperative laboratory results, ejection fraction and Euroscore II (Tables 1 & 2).

Variable	Early Group	Late Group	P value
Gender male	17 (77.3) 6 (22.7)	22 (68.6) 5 (17.9)	0.63
Age	52 ± 14.2	54 ± 14.1	0.65
Weight	78.8 ± 19.8	72.8 ± 16	0.25
Height	169.3 ± 5.3	167.1 ± 9.2	0.24
Smokers	6 (27.3)	6 (21.4)	0.50
Serum creatinine	114.59 ± 39.9	106.7 ± 45.7	0.53
Normal liver enzymes	21 (95.5)	23 (82.1)	0.18
≤double normal	1 (4.5)	2 (3.6)	0.86
>double normal	1 (0)	2 (14.3)	0.09
Ejection fracyion	50 ± 11.8	44 ± 11	0.17
Hemoglobin	12.99 ± 1.9	12.7 ± 2.7	0.73
Platelets count	221.18 ± 49.6	192.4 ± 58.7	0.07
Fibrinogen level	2.314 ± .38	2.15 ± .24	0.08
Euroscore II	11.5 ± 4.8	12.4 ± 6.6	0.15

Table 1: Patients demographics and preoperative variables among the studied groups.

Variable	Early Group	Late Group	P value
Elective	12 (50)	18 (64.3)	0.18
Urgent	7 (31.8)	3 (10.7)	
emergency	4 (18.2)	6 (25)	
Redo surgery	6 (27.3)	8 (28.6)	0.92
CABG	13 (59.1)	10 (35.7)	0.06
Valve surgery	5 (22.7)	9 (32.1)	0.05
CABG + valve	2 (4.5)	7 (28.6)	0.33
Other	3 (13.6)	1 (3.6)	
Non-anticoagulant	16 (68.2)	20 (75)	0.50
Heparin	6 (27.3)	7 (25)	0.41
Warfarin	1 (4.5)	0 (0)	0.43
Non-antiplatelet	11 (45.5)	10 (35.7)	0.76
Aspirin	11 (5o)	15 (57.1)	0.76
Clopidogrel	1 (4.5)	2 (7.1)	0.46
Preoperative IABP	2 (9.1)	3 (17.9)	0.32
Preoperative inotropic	2 (9.1)	3 (14.3)	0.46
Preoperative CCU admission	2 (9.1)	4 (14.3)	0.46

Table 2: Preoperative surgical characteristics among the studied groups. CABG: Coronary artery bypass grafting surgery, IABP: Intra aortic balloon pump, CCU: Coronary care unit.

Also there was no statistical significate difference in data collected for the intraoperative period between early and late group as cardiopulmonary bypass time was (189 ± 29.9 min) in early group and was (201.7 ± 86) in late group, We found statistically significant differences when we compared postoperative blood loss. Data showed less postoperative blood loss 1700 ml (825-1800) in the early group versus 2427ml (1200-3875) in the late group P value

0.001 (Figure 1). As to PRBCs transfused in the postoperative period 3.67 ± 3.1 units were transfused in the early group and 6.29 ± 4.3 units in the late group P value 0.02. Early group was transfused 4.58 ± 1.8 units of FFP while late group transfused 8.9 ± 6.3 units P value 0.02. Less platelets were transfused in the postoperative period in the early group and it was statistically significant lower when compared with the late group 8.8 ± 5.2 units for early group and 13.7 ± 6.7 units in late group with P value 0.02. Rate of re-exploration in the early group was 1.2 ± 0.4 in early group and 1.6 ± 0.5 in late group with P value 0.02 (Table 3).
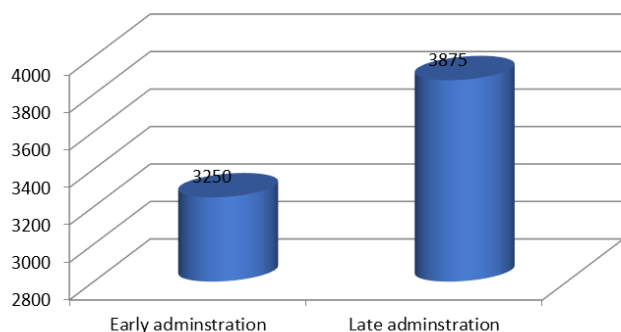
Total postoperative Blood Loss (ml)

Figure 1: Comparison of total amount of postoperative blood loss in ml in both groups.

There was no difference in the length of mechanical ventilation or length of hospital stay but length of intensive care unit stay was longer in the late group 9.39 ± 9.98 days in late group and 4.36 ± 2.77 days in early group p value 0.045 (Table 3).

Variable	Early group	Late group	P value
Re-exploration	1.2 ± .4	1.6 ± .5	0.02
Thrombo-embolic complication	0 (0)	0 (0)	--
Neurologic complication	0 (0)	1 (3.6)	0.56
Length of ventilation	1.55 ± .59	1.68 ± .77	0.12
Length of ICU stay	4.36 ± 2.77	6.39 ± 9.98	0.045
Length hospital stay	14 ± 11.6	14.2 ± 21.7	o.98
Mortality	1 (4.5)	2 (8.4)	0.19

Table 4: Postoperative outcomes among the studied groups.

Discussion

Severe bleeding is one of the most common complications following cardiac surgery. It can be due to one or more contributing factors. Incomplete surgical hemostasis, residual heparin effect after cardiopulmonary bypass, clotting factor depletion, hypothermia, hemodilution (dilutional thrombocytopenia and coagulopathy), or platelet abnormalities (platelet dysfunction and thrombocytopenia) were known as the most common causes [16]. Massive transfusion, historically defined as the replacement by transfusion of 10 units of red cells in 24 hours, as a response to massive and uncontrolled hemorrhage. With development of more rapid and effective strategies, alternative definitions were declared such as transfusion of three units of packed red blood cells over one hour.

It is more sensitive in identifying patients who need more concerns of transfusing blood products because of uncontrolled hemorrhage [17]. Massive transfusion involves the selection of the appropriate amounts and types of blood components to be administered and requires consideration of a number of issues during management strategies including volume status, tissue oxygenation, management of bleeding and coagulation abnormalities, as well as changes in ionized calcium, potassium, and acid-base balance.

Massive transfusions are in a subset analysis of a large randomized controlled trial of complex cardiac surgeries requiring repeat midline sternotomy, patients receiving transfusion of more than 5 units of RBCs had a threefold excess mortality if they did not also receive 5 units of plasma [18]. All efforts should be done to minimize massive transfusions to avoid the associated hemostatic and metabolic complications [19].

The transfusion practice varies widely in cardiac surgery as reported by Australian and New Zealand society of cardiac and thoracic surgeons, PRBCs were used in 22- 67 % of patients, platelets 11-39%, FFP 11-48% and cryo 1-20% [20]. In our study, there was statistically significant less postoperative blood loss 1700 ml (825-1800) in the early group and 2427ml (1200-3875) in the late group P value 0.001. Miskolczi et al. found that the effect of rFVIIa may be enhanced if it is given early in the course of blood loss.

Significant delay in the use of rFVIIa can be avoided because a temporary reduction in bleeding does not reduce mortality [21]. Safani et al. 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 [22]. Romagnoli et al. in two reports 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 [23-24]. There was statistically significant less postoperative need for blood and blood products transfusion (PRBCs given in the postoperative period was 3.67 ± 3.1 units in the early group and 6.29 ± 4.3 units in the late group P value 0.02. Early group was transfused 4.58 ± 1.8 units of FFP while late group transfused 8.9 ± 6.3 units P value 0.02. Platelets given in the postoperative period in the early group were also significantly less than the late group 8.8 ± 5.2 units for early group and 13.7 ± 6.7 units in late group with P value 0.02). Andersen et al 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 [25]. Andersen and his colleagues study matches with our study as regard less bleeding and less transfusion of blood products if rFVIIa given early, in the same time the need of rFVIIa repeated doses was higher if FVII give late (Table 4).

In a survey of UK practice in using rFVIIa in management of intractable hemorrhage, Biss and Hanley found wide variability in dose regimen [26]. In our study we found that dose of rFVIIa was 3.83 ± 1.3mg in early group and $3.53 \pm .84$ in late group with P value 0.33. FVII was give twice in one patient of the early group while in late group three patients given a second dose of FVII and one patient was given 3 doses (Table 4).

Variable	Early group	Late group	P value
FVII dose in mg	3.83 ± 1.3	$3.53 \pm .84$	0.33
One dose FVII	21 (95.5)	25 (89.3)	0.61
Two doses FVII	1 (4.5)	3 (7.1)	0.50
Three doses FVII	0 (0)	1 (3.6)	0.34
Re-exploration	$1.2 \pm .4$	$1.6 \pm .5$	0.02

Table 3: Postoperative rVII administration.

Conclusion

Early administration of rFVIIa in the management of severe bleeding following cardiac surgery was associated with decreased blood loss, decreased the need for blood and blood products transfusion and decreased Incidence of Re-exploration. Long-term safety remains unclear.

Acknowledgment

References

1. Agnese Ozolina, Eva Strike. Vladimirs Harlamovs and Nora Porite: Excessive Bleeding After Cardiac Surgery in Adults: Reasons and Management. ACTA 2009.
2. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. 2014; 147: 1458-1463.
3. Despotis GJ, Filos KS, Zoys TN, et al. Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements. Anesth Analg. 1996; 82: 13-21.
4. Nuttal GA, Oliver WC, Ereth MH, et al. Comparison of blood-conservation strategies in cardiac surgery patients at high risk of bleeding. Anesthesiology. 2000; 92: 674-682.
5. Aly Makram Habib, Ahmed Yehia Mousa, Zohair Al-Haleesc, et al. Recombinant activated factor VII for uncontrolled bleeding postcardiac surgery. J Saudi Heart Assoc. 2016; 28: 222-231.
6. Aly Makram Habib. Comparison of low- and high-dose recombinant activated factor VII for postcardiac surgical bleeding. Indian J Crit Care Med. 2016; 20: 497-503.
7. Warren O, Mandal K, Hadjianastassiou V, et al. Recombinant activated factor VII in cardiac surgery: A systematic review. Ann Thorac Surg. 2007; 83: 707-714.
8. Welsby IJ, Monroe DM, Lawson JH, et al. Recombinant activated factor VII and the anaesthetist. Anaesthesia. 2005; 60: 1203-1212.
9. Hesham R. Recombinant Activated Factor VII Significantly Reduces Transfusion Requirements in Cardiothoracic Surgery. Drugs R D. 2015; 15: 187–194.
10. Roberts, H.R. Thoughts on the mechanism of action of FVIIa, 2nd Symposium on New Aspects of Hemophilia Treatment, Copenhagen, Denmark, 1991, 153-156.
11. Hedner U. Dosing and monitoring NovoSeven treatment. Haemostasis. 1996; 26: 102-108.
12. Hoffman M. A cell-based modelof coagulation and the role of factor VII. Blood Rev. 2003; 17: 1-5.
13. Haemostasis Registry Final Report. Ten years of data on the use of recombinant activated factor VII in Australia and New Zealand. Available from: http://www.calembeena.com.au/HR_Final%20Report.pdf. Accessed July 2014.
14. Logan AC, Yank V, Stafford RS. Off-label use of recombinant factor VIIa in U.S. hospitals: analysis of hospital records. Ann Intern Med. 2011; 154: 516-522.
15. Levi M, Levy JH, Andersen HF, et al. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010; 363: 1791-1800.
16. Woodman RC, Harker LA. Bleeding complications associated with cardiopulmonary bypass. Blood. 1990; 76: 1680-1697.
17. Savage SA, Sumislawski JJ, Zarzaur BL, et al. The new metric to define large-volume hemorrhage: results of a prospective study of the critical administration threshold. J Trauma Acute Care Surg. 2015; 78: 224-229.
18. Delaney M, Stark PC, Suh M, et al. Massive Transfusion in Cardiac Surgery: The Impact of Blood Component Ratios on Clinical Outcomes and Survival. Anesth Analg. 2017; 124: 1777-1782.
19. Collins JA. Problems associated with the massive transfusion of stored blood. Surgery. 1974; 75: 274-295.
20. McQuilten ZK, Andrianopoulos N, Wood EM, et al. Transfusion practice varies widely in cardiac surgery: Results from a national registry. J Thorac Cariovasc Surg. 2014; 147: 1684-1690.
21. Miskolczi S, Vaszily M, Papp C, et al. Our experience with recombinant activated factor VII (Novo Seven) in the high risk cardio surgical patients with bleeding complication. Magy Seb. 2008; 61: 45-47.
22. Safani M, Drachenberg MR, Ferro ET, et al. Low-dose recombinant activated factor VII (rFVIIa) for excess hemorrhage after cardiac operation. Ann Thorac Surg. 2015; 99: 1865-1870.
23. Romagnoli S, Bevilacqua S, Gelsomino S, et al. Small-dose recombinant activated factor VII (NovoSeven) in cardiac surgery. Anesth Analg. 2006; 102: 1320-1326.
24. Gelsomino S, Lorusso R, Romagnoli S, 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.
25. Andersen ND, Bhattacharya SD, Williams JB, et al. Intraoperative use of low-dose recombinant activated factor VII during thoracic aortic operations. Ann Thorac Surg. 2012; 93: 1921-1928.
26. Biss TT, Hanley JP. Use of recombinant factor VIIa in the management of intractable haemorrhage: a survey of current UK practice. Br J Haematol 2007; 138: 126.