

# Prophylactic Administration Of Recombinant Activated Factor Vii In Coronary Revascularization Surgery

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## Citation

M Essam. *Prophylactic Administration Of Recombinant Activated Factor Vii In Coronary Revascularization Surgery*. The Internet Journal of Anesthesiology. 2006 Volume 13 Number 1.

## Abstract

**Background:** The objective of this clinical trial is to study the effectiveness of administering recombinant activated factor VII (rFVIIa) in reducing the amount of bleeding and the need for homologous blood & products transfusion in cardiac surgical coronary revascularisation procedures done under cardiopulmonary bypass (CPB).

**Methods:** In a randomised controlled prospective observational study, 30 patients scheduled for elective cardiac revascularisation under CPB. The patients were randomly allocated into two groups. Group I (control group) received no rFVIIa was following CPB. Group II (study group) a dose of 90ug/Kg of rFVIIa was administered following weaning off CPB. The total amount of chest tube drain during the first 24 hours following surgery was recorded as well as the qualitative and quantitative assessment of homologous blood & products transfusion.

Serial analysis of haematological parameters including haemoglobin level and coagulation test in a definite times were recorded as follow: To = baseline readings prior to CPB, T1 = off CPB after protamine administration and before administration of the study drug, T2 = on coronary intensive care unit (CICU) admission, T3 = 12 hours post CICU admission, T4 = 24 hours post CICU admission.

**Results:** Considering the total chest tube drainage, mean values showed statistically significant results ( $P=0.001$ ). Homologous blood and products transfusion were statistically lower in the study group ( $P<0.05$ ). The mean values for haematological assessment showed statistically lower INR values at CICU admission and 12 hrs post CICU admission ( $P<0.05$ ). Also, the PTT mean values were statistically lower at same timings ( $P<0.05$ ).

**Conclusion:** In conclusion the prophylactic use of rFVIIa in patients undergoing coronary revascularisation surgery under CPB had remarkable significant results on both the amount of postoperative bleeding as well as the amount of blood and products transfusion in regard to reducing postoperative bleeding tendency and hence blood transfusion.

## INTRODUCTION

Cardiac surgery associated with CPB can produce major haemostatic alterations that result in excessive postoperative bleeding<sub>1</sub>. Many factors are responsible for the complex haemostatic defect, including hypothermia, hemodilution, activation of the coagulation, fibrinolytics, and inflammatory pathways<sub>1</sub>. The use of anticoagulant agents, low-molecular weight heparin, and platelet inhibitors may also potentiates bleeding. Furthermore, technical aspects of cardiac procedures may contribute to bleeding; including the complexity of procedures, repetitive or combined operations,

duration of CPB time > 2.5 hours and the use of anticoagulant or antiplatelet agents may also contribute to bleeding<sub>2</sub>. Extensive homotransfusion of blood products has been associated with many adverse events, including bacterial infection, viral transmission, volume overload and increased mortality. The ability to reduce intractable perioperative bleeding could potentially be advantageous in reducing homologous transfusions, re-operation and mortality; any agent capable of reducing transfusion requirements could therefore be very useful<sub>3</sub>. The incidence of excessive postoperative bleeding in cardiac surgery

reaches around 5 to 7% with blood loss > 2 L within the first 24 hours postoperatively <sup>4</sup>. Early postoperative re-exploration due to bleeding and or tamponade reveals a surgically manageable source of bleeding in less than 50% of cases. However, surgical revision may be associated with multiple negative outcomes, such as increased mortality, prolonged mechanical ventilation, and higher rates of renal failure, postoperative arrhythmia, and infectious complications <sup>5</sup>. The use of therapeutic doses of rFVIIa is currently suggested for the management of life-threatening postoperative bleeding refractory to both surgical intervention and conventional pharmacotherapy. Recombinant FVIIa is a potent procoagulant active at sites of tissue damage which acts locally without causing general hypercoagulation <sup>6</sup>. Therapeutic dosage of rFVIIa results in it's binding to most tissue factor molecules with initiation of the extrinsic pathway of the coagulation cascade which leads to activation of maximum quantities of factor X with subsequent massive generation of thrombin. At the same time, factor IX of the procoagulation activity increases <sup>6</sup>.

The aim of the present work is to study the effectiveness of administering rFVIIa in reducing the amount of bleeding and the need for homologous blood and or products transfusion following cardiac surgical procedures performed under CPB.

## **PATIENTS & METHODS**

This study took place at King Fahad Cardiac Centre, King Saud University, Saudi Arabia. After obtaining hospital ethics committee approval and patient's informed consent 30 patients were studied. In this randomised controlled prospective observational study. Patients were scheduled to undergo elective cardiac revascularisation procedure that was previously determined to be under CPB whether by the tepid CPB method or by the on pump beating heart technique. Randomisation was established through sealed envelopes. Exclusion criteria included patients with known medical history of any haematological disorders, receiving clopidogrel therapy till night of surgery, lengthy CPB with > 120 min, or patients subjected for re-exploration. Patients were randomly allocated into two groups. Group I (control group) received no rFVIIa following CPB. Group II (study group) received a dose of 90ug/Kg of rFVIIa following weaning off CPB. All patients received standard anaesthesia and perioperative care according to the standard protocol in our centre within practice of the range of consultant anaesthetists and surgeons involved. This included the use of a standardized anticoagulation regimen and a cell-salvage device.

The anticoagulation regimen comprised heparin 300 IU/kg to achieve activated clotting time (ACT) >400 s prior to CPB, if not achieved, further boluses of heparin

100 IU/kg were administered. Intraoperative cell salvage of shed blood was used from skin incision until closure of the sternum at the completion of surgery. The bypass flow was 2.4 L/min/m<sup>2</sup> and the trigger for the transfusion of own blood was haemoglobin concentration <7 g/dl. Mean arterial pressures were maintained between 50 and 80 mm Hg using phenylephrine. After re-warming and completion of surgery patients were weaned from the CPB machine. After termination of CPB, protamine 3 mg/kg was given. Then patients in study group received rFVIIa 90 ug/kg. After aortic decannulation the residual volume within CPB circuit was drained into the cell-salvage device. Subsequently, this blood and salvaged shed blood were washed and centrifuged by the cell-salvage device and then re-transfused to the patient.

The total amount of chest tube drain during the first 24 hours following surgery was recorded as well as the qualitative and quantitative assessment of homologous blood and or products transfusion.

Serial analysis of haematological parameters including haemoglobin level and coagulation tests in a definite data points performed as follow: To = baseline readings prior to CPB, T1 = off CPB after protamine administration and before administration of the study drug, T2 = on CICU admission, T3 = 12 hours post CICU admission, T4 = 24 hours post CICU admission.

Descriptive analysis was done using the SPSS statistical package version 13.0. Data were presented as mean ± SD and numbers. Groups were compared using the parametric or the non-parametric versions of t-test with Welch correction. Nominal data were compared using the chi-square test or alternatively by fisher's exact test. P value < 0.05 was considered significant.

## **RESULTS**

Results showed that the two groups were comparable regarding their demographic data and time of CPB (table 1). The chest tube drainage mean value in the study group was significantly lower than the control group (P< 0.05) (table 2). Also the mean value of homologous blood and products transfusion were statistically lower in the study group versus the control group (table 2). Regarding the mean values for haematological assessment, results showed statistically

lower INR values at CICU admission and 12 hrs post CICU admission ( $P<0.05$ ) (table 3).

**Figure 1**

Table 1: Patient Demographic data (Mean  $\pm$ SD)

	Control Group n = 15	Study Group n = 15	p value
Age (yr)	61.4 $\pm$ 4.86	59.46 $\pm$ 6.45	0.124
Weight ( Kg )	79 $\pm$ 6.164	79.2 $\pm$ 6.95	0.725
Height ( cm )	167.4 $\pm$ 6.82	167.1 $\pm$ 6.03	0.604
CPB Time (min )	100.8 $\pm$ 9.8	100.2 $\pm$ 8.572	0.454

**Figure 2**

Table 2: Chest tube drain in 24 hr and transfusion products in ml (Mean  $\pm$  SD)

	Control Group n= 15	Study Group n= 15	p value
Chest tube drain in 24 hrs ( ml )	620.33 $\pm$ 108.33 *	435 $\pm$ 93.86 *	0.001 *
PRBC's	516.66 $\pm$ 175.93 *	316.6 $\pm$ 333.6*	0.047 *
FFP	270 +/- 181.06 *	60 $\pm$ 94.8 *	0.004 *
Platelets	106.6 $\pm$ 67.78 *	40 $\pm$ 68.6 *	0.021 *

\* Significant  $P<0.05$

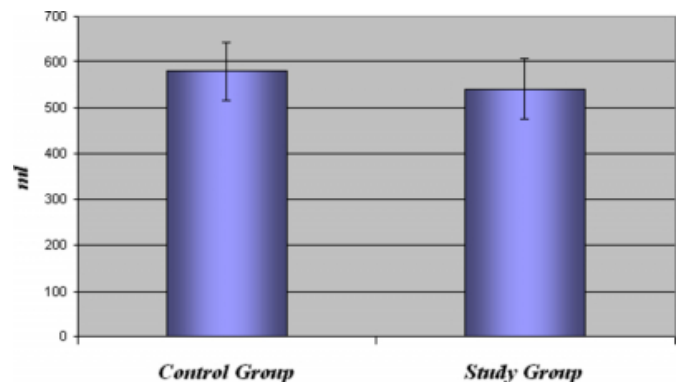
**Figure 3**

Table 3: Haematological Assessment (Mean  $\pm$ SD) (P

	Control Group N= 15	Study Group N= 15	p value
<b>T0 = Baseline</b>			
Haemoglobin (g/dl)	12.56 $\pm$ 1.22	12.56 $\pm$ 0.79	0.985
INR	1.04 $\pm$ 0.12	1.02 $\pm$ 0.108	0.677
PTT (sec)	33.2 $\pm$ 5.41	32.06 $\pm$ 4.18	0.284
Fibrinogen (g/l)	3.04 $\pm$ 0.56	3.11 $\pm$ 0.64	0.533
<b>T1 = Off CPB</b>			
Haemoglobin (g/dl)	8.53 $\pm$ 0.72	8.66 $\pm$ 0.47	0.34
INR	2.38 $\pm$ 0.4	2.53 $\pm$ 0.45	0.168
PTT (sec)	54.11 $\pm$ 2.36	52.23 $\pm$ 14.02	0.6818
Fibrinogen (g/l)	2.12 $\pm$ 0.38	2.2 $\pm$ 0.34	0.118
<b>T2 = CICU Admission</b>			
Haemoglobin (g/dl)	9.27 $\pm$ 0.82	9.26 $\pm$ 0.68	0.959
INR	1.4 $\pm$ 0.17 *	1.26 $\pm$ 0.09 *	0.018 *
PTT (sec)	53.86 $\pm$ 8.71 *	49 $\pm$ 6.32 *	0.04 *
Fibrinogen (g/l)	2.21 $\pm$ 0.26	2.35 $\pm$ 0.32	0.196
<b>T3 = 12 hrs CICU</b>			
Haemoglobin (g/dl)	9.51 $\pm$ 0.63	9.71 $\pm$ 0.61	0.098
INR	1.52 $\pm$ 0.19 *	1.3 $\pm$ 0.12 *	0.004 *
PTT (sec)	49.86 $\pm$ 13.6 *	39.06 $\pm$ 8.2 *	0.001 *
Fibrinogen (g/l)	2.26 $\pm$ 0.25	2.33 $\pm$ 0.26	0.334
<b>T4 = 24 hrs CICU</b>			
Haemoglobin (g/dl)	9.03 $\pm$ 2.26	9.9 $\pm$ 0.74	0.159
INR	1.14 $\pm$ 0.09	1.1 $\pm$ 0.13	0.337
PTT (sec)	39.6 $\pm$ 6.07	38.67 $\pm$ 9.43	0.751
Fibrinogen (g/l)	2.28 $\pm$ 0.17	2.34 $\pm$ 0.23	0.322

**Figure 4**

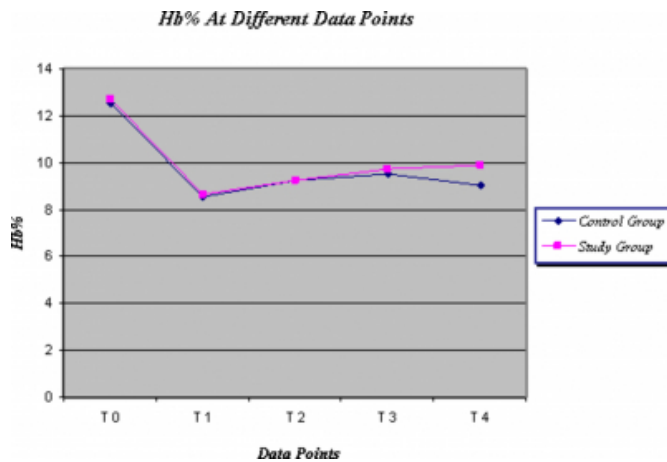
Figure 1: Trend of haemoglobin concentration in both groups



Also, the PTT mean values were statistically lower at same timings in the study group versus the control one ( $P<0.05$ ) (table 3). Volume of transfused cell saved blood was comparable in both groups (figure 2).

**Figure 5**

Figure 2: Volume of transfused cell-saved own blood in both groups



## DISCUSSION

Excessive postoperative bleeding is a drastic complication occurring in 5–7% of cardiac surgeries with CPB, which often requires re-exploration and the transfusion of large quantities of red blood cells, plasma and platelets <sup>4</sup>. Increased postoperative morbidity and mortality are also associated with excessive bleeding, with the need for re-exploration, and are probably related to the massive transfusion of blood products. Although haemostatic agents as anti-fibrinolytics are frequently used, yet they may not be effective in all cases <sup>7</sup>.

Relatively little is known about the molecular mechanisms by which rFVIIa induces the formation of a stable haemostatic plug <sup>6</sup>. Most researchers in the field agree that rFVIIa has no direct effect on haemostatic plug formation, but exerts an effect by enhancing thrombin generation at sites of tissue injury. However, controversy exists regarding the mechanisms by which this occurs, specifically the role and source of the protein tissue factor (TF). When vessel injury occurs in normal subjects, sub-endothelial cells that express TF are exposed to the blood. Subsequently TF binds to and activates FVII. The resulting TF-FVIIa complex catalyzes the conversion of factor X into its active form (Xa) leading to thrombin formation and platelet activation. This creates a surface that supports the binding of coagulation factors and thereby facilitates the full thrombin burst necessary for haemostasis <sup>6</sup>.

Bleeding after cardiac surgery is complex in origin. Provided that adequate surgical haemostasis has occurred, the residual bleeding results from a mixture of hypothermia, platelet dysfunction and haemodilution of red blood cells and

coagulation factors. The formation of a stable fibrin plug at the site of endovascular disruption is a complex event, with the interaction of circulating VIIa and tissue factor playing a key initiating role <sup>8</sup>.

In this pilot study, results showed that prophylactic use rFVIIa significantly reduces both the excessive post-operative bleeding and the amount needed of homologous blood and products transfusion as explained to an extent by the statistically significant improvement in coagulation profile of the study group in the postoperative period. Although haemoglobin concentrations were comparable in both groups, yet this was achieved in the control group with a significantly higher volume of PRBCs transfusion.

The prophylactic use rFVIIa was studied by Diprose and colleagues on 20 adult patients undergoing complex non-coronary cardiac surgery <sup>9</sup>. At cessation of CPB, they neutralized heparin and randomized patients to either rFVIIa 90 ug/kg or an equivalent dose of normal saline. Blood products and anti-fibrinolytics were then administered according to protocol. The treated group received a total of 13 units of allogeneic blood products compared with 105 units in the placebo group and they concluded that rFVIIa has exciting potential as a prophylactic haemostatic agent <sup>9</sup>. In another case series of cardiac surgical patients with intractable postoperative bleeding done by Vanek and colleagues, they reported that Administration of recombinant activated factor VII was associated with significant reduction in blood loss ( $P < 0.05$ ) and shortening of INR and APTT in laboratory tests <sup>4</sup>.

The magnitude of research regarding rFVIIa in cardiac surgical practice had reached a level that enables Oliver W. and colleagues to run a systematic review, but with a limitation of that the majority of studies included were small non-randomized studies <sup>10</sup>. While they end into a conclusion that recombinant factor VIIa is a potent prohemostatic agent, and it possesses a role for cessation of life-threatening refractory haemorrhage associated with cardiac surgery. They suggested that there is currently little evidence to suggest a prophylactic role, and well-designed, multicenter, randomized controlled trials are required to definitively answer questions on the cost effectiveness, appropriate dosing regime, and safety profile of rFVIIa within specific patient groups<sup>10</sup>. From the author point of view regarding the cost of rFVIIa, that in spite of being relatively high, yet it had to be weighed against the cost of blood and products transfusion, re-exploration of patients in the postoperative

period and length of stay in the CICU.

In conclusion prophylactic use of rFVIIa in this pilot study in patient undergoing coronary revascularisation surgery had remarkable results in reducing postoperative bleeding tendency and hence blood transfusion. However, another randomised study is required on large sample size to prove our results.

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