Prophylactic administration of recombinant activated factor VII in coronary revascularization surgery

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ABSTRACT

Objective: 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 and products transfusion in cardiac surgical coronary revascularization procedures done under cardiopulmonary bypass (CPB). **Methods:** In a randomized controlled prospective observational study, 30 patients were scheduled for elective cardiac revascularization under CPB. Patients were randomly allocated into two groups. In Group I (Control group), no rFVIIa was administered following CPB. In Group II (Study group), a dose of 90 ug/Kg of rFVIIa was administered following weaning off CPB. The total amount of chest tube drain during the 1st 24 h following surgery was recorded as well as the qualitative and quantitative assessments of homologous blood and products transfusion. Serial analysis of hematological parameters including hemoglobin level and coagulation test in a definite data points was done. T0=baseline readings prior to CPB, T1=off CPB after protamine administration and before administration of the study drug, T2=on Cardiac Intensive Care Unit (CICU) admission, T3=12 h post-CICU admission, and T4=24 h post-CICU admission. **Results:** Considering the total chest tube drainage, mean values showed statistically significant results with a *P* value of 0.001. Homologous blood and products transfusion were statistically lower in the study group. Regarding the mean values for hematological assessment, results showed statistically lower International Normalized Ratio values at CICU admission and 12 h post-CICU admission with a *P* value of 0.018 and 0.004, respectively. Also, the Partial Thromboplastin Time mean values were statistically lower at same timings with estimated *P* values of 0.04 and 0.001, respectively. **Conclusion:** It is concluded that the prophylactic use of rFVIIa in patients undergoing coronary revascularization surgery under the management of CPB had a remarkable significant results on both the amount of post-operative bleeding and the amount of blood and products transfusion.

Key words: *CABG, coronary revascularization, recombinant activated factor VII*

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INTRODUCTION

Cardiac surgery associated with cardiopulmonary bypass (CPB) can produce major hemostatic alterations that result in excessive post-operative bleeding.[1] Many factors are responsible for the complex hemostatic defect, including hypothermia, hemodilution, and activation of the coagulation, fibrinolytics, and inflammatory pathways.[1] The use of anticoagulant agents, low molecular weight heparins, and platelet inhibitors may also potentiate bleeding. Furthermore, technical aspects of cardiac procedures may contribute to bleeding, including the complexity of procedure(s), repetitive or combined operations, duration of CPB time exceeding 2.5 h, and the use of anticoagulant or antiplatelet agents.[2] 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-operatio, and mortality; any agent capable of reducing transfusion requirements could therefore be very useful.[3] The incidence of excessive post-operative

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bleeding in cardiac surgery reaches around 5-7% of patients and showing blood loss over 2 L within the 1st 24 h post-operatively.[4] Early post-operative re-exploration for bleeding/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, post-operative arrhythmia, and infectious complications.[5] The use of therapeutic doses of recombinant activated factor VII (rFVIIa) is currently suggested for the management of life-threatening post-operative bleeding refractory to both surgical intervention and conventional pharmacotherapy. rFVIIa is a potent pro-coagulant active site of tissue damage (with expression of the tissue factor (TF)): It acts locally without causing general hypercoagulation.[6] Therapeutic dosage of rFVIIa results in its binding to most TF molecules; initiation of the extrinsic pathway of the coagulation cascade leads in turn to activation of maximum quantities of factor X with subsequent massive generation of thrombin. At the same time, factor IX of the intrinsic pathway of the coagulation cascade is also activated and consequently, pro-coagulation activity increases.[6]

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

METHODS

This study took place at King Fahad Cardiac Centre, King Saud University, Saudi Arabia. After obtaining our hospital Research Review Board approval, the study was instituted by May 2006 and ends by November 2006. An informed patient consent was taken from eligible patients before being enrolled to the study. In a randomized controlled prospective observational study, 30 patients scheduled for elective cardiac revascularization procedure that was previously determined to be under the management of CPB whether by the tepid CPB method or by the on-pump beating heart technique were enrolled to the study. Randomization of patients was taken through sealed envelopes. Exclusion criteria included patients with known medical history of any hematological disorder, clopidogrel therapy till night of surgery, lengthy CPB time >120 min, and patients subjected for re-exploration as carrying possibility of surgical cause for bleeding. Patients were randomly allocated into two groups. In Group I (Control group), no rFVIIa was administered following CPB. In Group II (Study group), a dose of 90 ug/Kg of rFVIIa was administered following weaning off CPB. All patients received standard anesthesia and perioperative care according to the standard protocol in our center within practice of the range of consultant anesthetists 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 a Celite activated clotting time (ACT) >400 s prior to CPB. If this ACT was 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. On CPB, the bypass flow was 2.4 L/min/m^2 and the trigger for the transfusion of own blood was a hemoglobin concentration <7g/dl. Mean arterial pressures were maintained between 50 and 80 mm Hg using phenylephrine. After re-warming and completion of the aspects of surgery requiring CPB, patients were weaned from the CPB machine. After termination of CPB, heparin was neutralized using protamine 3 mg/kg. Following this, patients in study group received rFVIIa 90 ug/kg. After aortic decannulation, the residual volume within the 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 1st 24 h following surgery was recorded as well as the qualitative and quantitative assessments of homologous blood and products transfusion. Serial analysis of hematological parameters including hemoglobin level and coagulation tests in a definite data points was done. T0=baseline readings prior to CPB, T1=off CPB after protamine administration and before administration of the study drug, T2=on Cardiac Intensive Care Unit (CICU) admission, T3=12 h post-CICU admission, and T4=24 h post-CICU admission.

Statistical analysis

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* values less than 0.05 were considered significant.

RESULTS

Results showed that the two groups were comparable regarding their demography and CPB time [Table 1]. Considering the total chest tube drainage, mean values showed statistically significant results with a *P* value of 0.001 [Table 2]. Homologous blood and products transfusion

were statistically lower in the study group [Table 2]. Regarding the mean values for hematological assessment, results showed statistically lower INR values at CICU admission and 12 h post-CICU admission with a *P* value of 0.018 and 0.004, respectively [Table 3]. Also, the PTT mean values were statistically lower at same timings with estimated *P* values of 0.04 and 0.001, respectively [Table 3]. Volume of transfused cell saved blood was comparable in both groups [Figure 1].

DISCUSSION

Excessive post-operative 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.[4] Increased post-operative 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 hemostatic agents as antifibrinolytics are frequently used, yet they may not be effective in all cases.[7] Relatively, little is known about the molecular mechanisms by which rFVIIa induces the formation of a stable hemostatic plug.[6] Most researchers in the field agree that rFVIIa has no direct effect on hemostatic 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 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 hemostasis.[6]

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

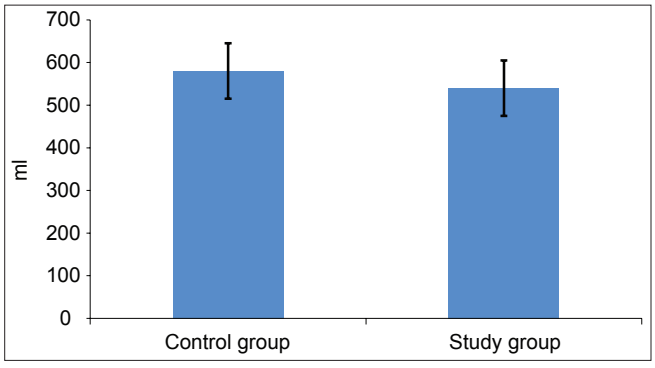

Figure 1: Volume of transfused cell saved own blood in both groups

Table 1: Patient demography (mean±SD)

	Control group *N*=15	Study group *N*=15	*P* value
Age	61.4±4.86	59.46±6.45	0.124
Weight (kg)	79±6.164	79.2±6.95	0.725
Height (cm)	167.4±6.82	167.1±6.03	0.604
CPB time (min)	100.8±9.8	100.2±8.572	0.454

CPB – Cardiopulmonary bypass

Table 2: Volume of total chest tube drain and transfusion products (mean±SD)

	Control group *N*=15	Study group *N*=15	*P* value
Total chest tube drain in 24 h (ml)	620.33±108.33*	435±93.86*	0.001*
Homologous transfusion products in ml			
PRBCs	516.66±175.93*	316.6±333.63*	0.047*
FFP	270±181.06*	60±94.8*	0.004*
Platelets	106.6±67.78*	40±68.6*	0.021*

*Statistically significant. *P*<0.05; PRBCs – Packed red blood cells; FFP – Freah frozen plasma

Table 3: Haematological assessment (mean±SD)

	Control group *N*=15	Study group *N*=15	*P* value
To=Baseline			
Haemoglobin (g/dl)	12.56±1.22	12.56±0.79	0.985
INR	1.04±0.12	1.02±0.108	0.677
PTT (s)	33.2±5.41	32.06±4.18	0.284
Fibrinogen (g/l)	3.04±0.56	3.11±0.64	0.533
T1=Off CPB			
Haemoglobin (g/dl)	8.53±0.72	8.66±0.47	0.34
INR	2.38±0.4	2.53±0.45	0.168
PTT (s)	54.1±12.36	52.23±14.02	0.6818
Fibrinogen (g/l)	2.12±0.38	2.2±0.34	0.118
T2=CICU Admission			
Haemoglobin (g/dl)	9.27±0.82	9.26±0.68	0.959
INR	1.4±0.17*	1.26±0.09*	0.018*
PTT (s)	53.86±8.71*	49±6.32*	0.04*
Fibrinogen (g/l)	2.21±0.26	2.35±0.32	0.196
T3=12 h CICU			
Haemoglobin (g/dl)	9.51±0.63	9.71±0.61	0.098
INR	1.52±0.19*	1.3±0.12*	0.004*
PTT (s)	49.86±13.6*	39.06±8.2*	0.001*
Fibrinogen (g/l)	2.26±0.25	2.33±0.26	0.334
T4=24 h CICU			
Haemoglobin (g/dl)	9.03±2.26	9.9±0.74	0.159
INR	1.14±0.09	1.1±0.13	0.337
PTT (s)	39.6±6.07	38.67±9.43	0.751
Fibrinogen (g/l)	2.28±0.17	2.34±0.23	0.322

*Statistically significant. *P*<0.05; INR – International normalised ratio; PTT – Partial thromboplastin time; CICU – Cardiac intensive care unit; CPB – Cardiopulmonary bypass

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 TF playing a key initiating role.[8] In this pilot study, results showed that prophylactic use rFVIIa significantly reduces both the excessive post-operative bleeding and the amount needed for homologous blood and products transfusion as explained to an extent by the statistically significant improvement in coagulation profile of the study group in the post-operative period. Although hemoglobin concentrations were comparable in both groups, yet this was achieved in the control group with a significantly higher volume of Packed Red Blood Cells transfusion.

The prophylactic use of rFVIIa was studied by Diprose and colleagues on 20 adult patients undergoing complex non-coronary cardiac surgery.[9] 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 antifibrinolytics 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 hemostatic agent.[9] In another case, series of cardiac surgical patients with intractable post-operative 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 a PTT in laboratory tests.[4] 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 that the majority of studies included were small non-randomized studies.[10] Although they end into a conclusion that recombinant factor VIIa is a potent pro-hemostatic agent, it possesses a role for cessation of life-threatening refractory hemorrhage 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.[10] From the author point of view regarding the cost of rFVIIa, 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 post-operative period, length of stay in the CICU, and not to mention the consequences of all those factors on patient morbidity.

It is concluded that the prophylactic use of rFVIIa in this pilot study in patient undergoing coronary revascularization surgery had a remarkable significant results in reducing postoperative bleeding and blood products transfusion, yet it is recommended to proceed with higher scale of large randomized controlled studies.

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