

The Use of Recombinant Activated Factor VIIa in the Management of Post Operative Bleeding in Cardiac Surgery; Our Experience at Queen Alia Heart Institute

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ABSTRACT

Objective: To describe our experience in the use of recombinant activated factor VII (Novoseven) in the management of post operative bleeding in cardiac surgery at Queen Alia Heart Institute / King Hussein Medical Center-Jordan.

Methods: A simple descriptive study at Queen Alia Heart Institute between January 2008 till December 2011 on a total of 160 patients who underwent open heart surgery and received recombinant activated factor VII (rfVIIa) was conducted. A specially designed medical record abstract form was used to collect demographic, surgical and hematological data. Simple descriptive statistics (mean, percentage, interquartile range) was used to describe the relevant data. T-test was used also for determining bleeding, transfusion and coagulation profile before and after rfVIIa treatment. P value was considered statistically significant if <0.005 .

Results: The rate of recombinant factor VIIa use was 0.02% (number of patients received Novoseven/ total number of operations carried out). The mean dose of rfVIIa used was $65\mu\text{g}/\text{kg}$ where 152 patients (95%) of the study group received single dose that stopped their bleeding. A total of 135 (84%) patients received their dose in the Intensive Care Unit while 25 patients (16%) received their dose in the operating theater. After the administration of recombinant factor VIIa it was clear that the amount of blood loss significantly decreased and the usage of the blood and its products was appreciably lower with the therapy than before it ($p<0.001$). Clinical outcome showed 4 deaths among patients received Novoseven (2.5% mortality rate) although this was expected because of previous risky preoperative or intraoperative course. None of our patients developed thromboembolic complications.

Conclusions: Recombinant Factor VIIa appears to be safe and effective in controlling nonsurgical life threatening bleeding in cardiac surgery. It has been able to decrease the amount of blood loss, restoring hemostasis and reduce the need for further blood transfusion.

Key words: Bleeding, Blood transfusion, Cardiac Surgery, Recombinant Factor VIIa

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Introduction

Surgery in general is associated with some complications and one of them is bleeding which ranges from mild to severe form and accordingly increases the mortality, morbidity and hospital stay.^(1,2)

Bleeding is a serious complication after cardiac

surgery where 3-5% of patients require reexploration and up to 7% lose more than 2 liters of blood in the first 24 hours.⁽³⁻⁵⁾

After exclusion of the surgical causes bleeding due to impaired hemostasis may be attributed to many factors where hemodilution, excessive fibrinolysis, platelets dysfunction, residual heparin and effect of hypothermia could be some causes that increase

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bleeding on microvascular level.^(3,4,6) Identification of patients at high risk of bleeding and testing new modalities for blood loss management will reduce the burden of coagulopathy and excessive blood loss.⁽⁷⁾

Optimization of the transfusion of the blood and its products should be considered to decrease the risks.⁽⁸⁾

Procoagulant therapy including desmopressin acetate, aminocaproic acid, tranexamic acid, aprotinin (withdrawn from the market in 2007) and activated prothrombin complex concentrates have not been so widely adopted into practice in the perioperative surgical management except for the emerging of rfVIIa with ever increasing use by wide range of surgeons.⁽⁹⁾

Recombinant Factor VIIa exerts its action through two mechanisms both of them act on the site of local injury (tissue damage) to restrict the coagulation activation. First one by adherence to the tissue factor forming a complex that activates the remaining coagulation cascade. The second mechanism through binding to activated platelets which additionally direct the activation of factor X to the site of tissue injury. The thrombus formation generated by the activated factor X from the above two mechanisms will finally lead to the formation of fibrin network that is very essential to clot stabilization and secondary coagulation.⁽¹⁰⁾

The food and drug administration (FDA) approved its use in treating bleeding in patients with congenital hemophilia A (deficiency of factor VIII) or B (deficiency of factor IX) with inhibitors and congenital factor VII deficiency. Recently, it expands its use on prophylactic purposes for the above conditions as well as the acquired forms of hemophilia with inhibitors for factors VIII and IX.⁽¹¹⁾

The off label indications of Factor VIIa use gained a lot of interest in the last period as it became more available where it expands to be involved in the management of uncontrolled hemorrhage, prophylaxis and treatment response to massive intra and postoperative bleeding.⁽¹²⁾

It was clear that it can induce excellent hemostasis for intractable bleeding in vascular surgery as well as its known previous role in trauma and major surgery.⁽⁹⁾

Several reports have described the efficacy and safety of using recombinant activated factor VII for the management of intraoperative and post operative bleeding in cardiac surgery.^(3,5,6,10-18)

The aim of this study is to describe our experience in the use of recombinant activated factor VII (Novoseven) in the management of post operative bleeding in cardiac surgery at Queen Alia Heart Institute / King Hussein Medical Center.

Methods

A simple descriptive study at Queen Alia Heart Institute between January 2008 till December 2011 for a total of 160 patients who underwent open heart surgery and received recombinant activated factor VII (rf VIIa) was conducted. A specially designed medical record abstract form was used to collect demographic, surgical and hematological data. Simple descriptive statistics (mean, percentage, interquartile range) was used to describe the relevant data. T-test was used also for determining bleeding, transfusion and coagulation profile before and after rfVIIa treatment. P value was considered statistically significant if <0.005 .

The demographical, procedural, hematological data were abstracted from the patient's medical records; operating rooms and ICU database to assess the efficacy and safety of recombinant factor VIIa treatment.

Hematological database included activated partial thromboplastin time (APTT), International normalized ratio (INR), Prothrombin time (PT) and platelets count. Coagulation profiles were measured before and within 3-6 hours of recombinant factor VIIa administration.

The amounts of packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate as well as the volume of total blood loss before and after the administration were all monitored. The comorbidities, clinical outcome and associated complications were all registered. All of our patients in the study underwent cardiac surgery operations using cardiopulmonary bypass where standard institutional guidelines were always followed.

Cardiopulmonary bypass (CPB) was performed using a noncoated circuit and a membrane oxygenator. Heparin (5000 IU) was added to the CPB priming solution and initial intravenous dose of 300 IU/kg of heparin was administered.

Heparinization was monitored with a kaolin activated clotting time (ACT) measured every 30 minutes and ACT was maintained above 480 seconds with additional dose of 500IU Heparin intravenously if needed. Heparin was reversed using 1mg protamine sulphate for each 1mg of heparin. Reversal was assessed using heparinase treated ACT (normal <150 seconds), protamine was given based on the ACT where a ratio of 1.3mg protamine to 1mg heparin is always not exceeded. During cardiopulmonary bypass hematocrit is kept above 25mg/dl. Cardiopulmonary bypass was conducted at 33°C for coronary artery bypass grafting or valvular surgery. Antegrade crystalloid cardioplegia was

mainly used for myocardial protection while some surgeons prefer to use both antegrade and retrograde blood cardioplegia during their surgeries. For patients who underwent Aortic surgery for arch reconstruction, they were cooled to 18°C for a period of circulatory arrest of < 30 minutes. We considered the patient to have significant post operative bleeding if he postoperatively bleed >500cc in any hour or \geq 400 cc during each of any 2 successive hours or \geq 300cc in each of any 3 successive hours or by the end of the 4th or 5th post operative hour the patient has bleed 1000cc or 1200cc respectively. A protocol for management of significant bleeding at our hospital which depends on the hemodynamic status of the patients is shown in Fig. 1.

Triggers for transfusion was hemoglobin <10mg/dl for red cell concentrate, INR>1.5, plasma activated partial thromboplastin time >50 seconds or platelets < 100.000.

If after surgical exploration and substitution therapy patient is still having bleeding we give Novoseven (45,90 μ g/kg). For intraoperative severe uncontrolled nonsurgical bleeding some cases of redo surgery or in case of severe pericardial adhesions regardless proper packing and replacement therapy we also gave Novoseven. We used to correct the temperature and metabolic status before commencement of management.

The approval of the local ethical committee and a written consent was obtained from each patient. T-test was used also for determining bleeding, transfusion and coagulation profile before and after rfVIIa treatment. P value was considered as statistically significant if <0.005.

Results

Between January 2008-December 2011, 8786 cardiac surgery operations were performed out including 392 operations as reopening for bleeding. The reopening rate was around 4.5%. The mean age of the reopened patients was 59 years (range between 19-81years). The mean preoperative hemoglobin was 13.4mg/dl (range between 9-19mg/dl), average euroscore 3.66 (range between 2-8), average total pump time 118 minutes (range 54-242 minutes). The ICU stay, postoperative complications, total hospital stay was prolonged in comparison to the non-reopened patients.

Through the last 4 years, 160 patients were given Novoseven (134 male (84%), 26 females (16%)). The frequency of the patients who were given Novoseven to the total number of operations carried out was around 0.02%.

The demographic and surgical data of the 160 patients are shown in Table I. The decision to use recombinant factor VIIa was made by the surgical team after following the protocol in our institution. The yearly usage of factor VIIa is described in Fig. 2 where it showed ongoing increase from 2008 through 2010 even though the rate decreased once again in 2011 due to the drop off the total number of operations because of the ICU maintenance.

To ensure adequate media for the hemostasis, the blood products were always transfused before Novoseven administration. The mean dose of rfVIIa used was 65 μ g/kg and it was repeated if bleeding persists. A total 152 patients of the study group received single dose (95%), 7 patients received 2 doses (4.4%) and for only one patient we had to repeat the dose 3 times (0.6%).

One hundred and thirty-five patients (84%) received their dose in the ICU while 25 patients (16%) received their dose in the operating theater. The median time between the end of cardiopulmonary bypass and the first dose of Novoseven was 280 minutes, range (20-880minutes). After the administration of recombinant factor VIIa it was clear that the amount of blood loss significantly decreased. The range of the loss before Novoseven was given (1250cc-3050cc) with a median of 2100cc while after infusion the range declined to (500cc-1150cc) with a median of 750cc.

There was dramatic reduction in the requirements of the blood (packed red blood cells) and blood products (fresh frozen plasma (FFP), platelets, cryoprecipitate) as demonstrated in Table II; where average of 4 units of blood, 10 units of FFP, 10 units of platelets and 4 units of cryoprecipitate were transfused between the end of the bypass and before Novoseven administration.

The usage of the blood and its products was significantly lower with Novoseven therapy (packed red blood cells 1unit, range (0-3), FFP 1.3(0-6), Platelets 1.1(0-3), cryoprecipitate 0.5 (0-2)) than before it (packed red blood cells 4(2-8), FFP10 (8-16), platelets10 (6-16), cryoprecipitate4 (1-6)). P-value was <0.001. On the other hand there was no significant difference in the laboratory value except for the obvious reduction in the INR rates as shown in Table III.

Clinical outcome revealed 4 deaths (2.5%), one patient died in the operating room after intractable bleeding for complex arch reconstruction surgery. Two other patients died early from multisystem failure. The 4th patient died after massive stroke where he was known to have peripheral vascular

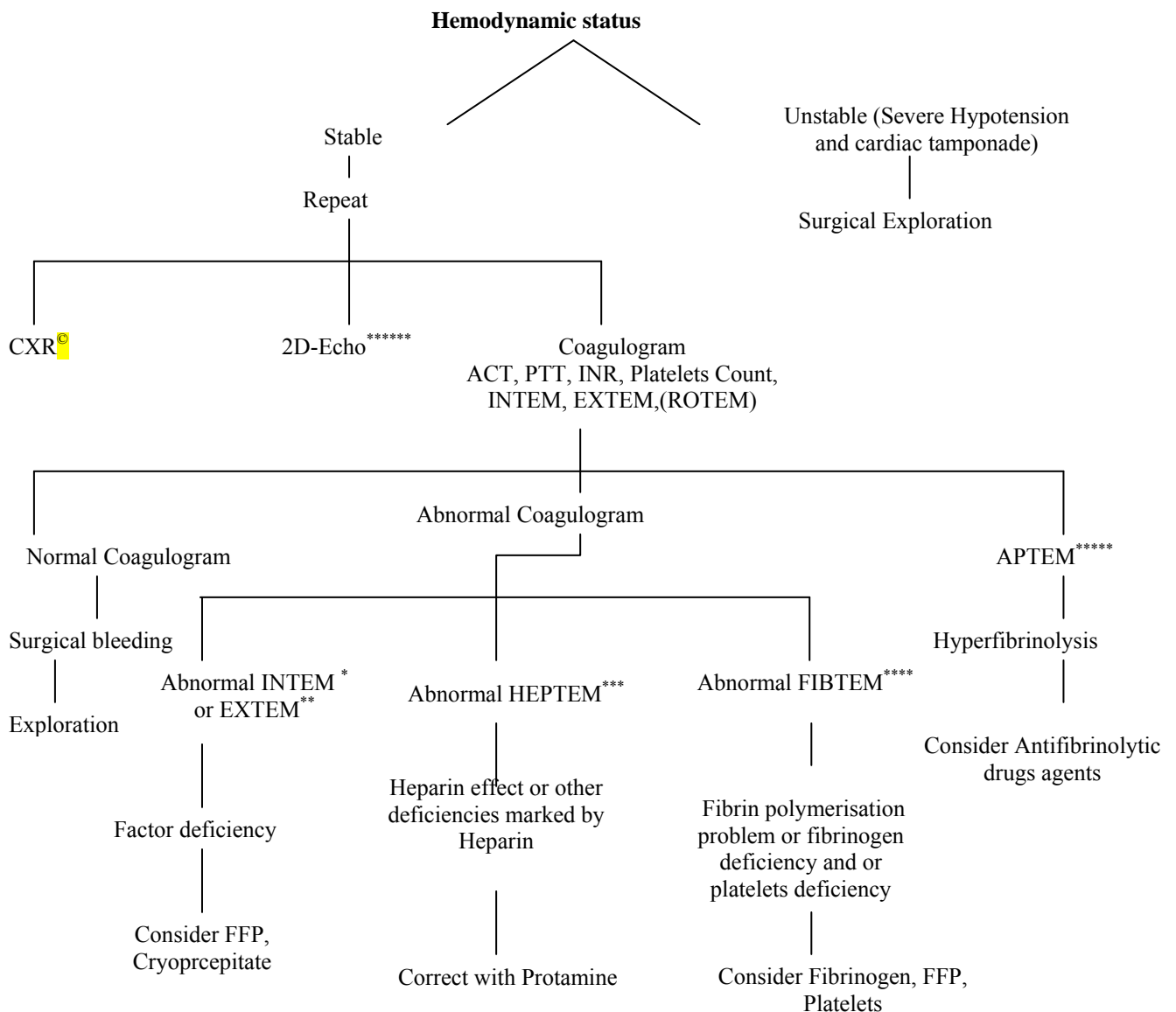


Fig. 1: Protocol for management of significant bleeding at QAHI

* **INTEM** is a screening test for the haemostasis system. It is used for therapeutic decisions regarding the administration of fresh frozen plasma, coagulation factors, fibrinogen or platelets.

** **EXTEM** is a screening test for the (extrinsic) haemostasis system

*** **HEPTEM** This assay represents an INTEM assay performed in the presence of heparinase, a heparin (or LMWH) degrading enzyme

**** **FIBTEM** test is an EXTEM based assay for the fibrin part of the clot

***** **APTEM** test is an EXTEM based assay in which fibrinolysis is inhibited by aprotinin in the reagent.

***** **2D-Echo** two dimensional echocardiography

© **CXR** Chest X Ray

- If after surgical exploration and substitution therapy patient is still having bleeding give Novoseven. For Intraoperative severe uncontrolled nonsurgical bleeding, in some cases of redosurgery or incase of severe pericardial adhesions regardless proper packing and replacement therapy also give Novoseven.

Table I: Demographic characteristics and surgical data of the patients received Novoseven (rf VIIa)

Feature	Data
Total Number of Patients	160
Age	Mean 61 ± 11 years Range 22-76
Gender	Male 134 (84%) Female 26 (16%)
Number of Diabetic patients	65 patients (41%)
Number of Hypertensive patients	41 patients (26%)
Average Body mass Index	26.5
Euroscore (additive)	Range 2-8 Average 3.5
Pump Time	Total (54-242 minutes) Average (118 minutes)

Table II: Bleeding and transfusions before and after rf VIIa

Item	Pre rf VIIa*	Post rf VIIa*	P value **
Bleeding	2100cc(1250cc-3050 cc)	750cc(500cc-1150cc)	P<0.001
Fresh Frozen plasma(FFP)	10(8-16)units	1.3(0-6)units	P<0.001
Platelets	10(6-16) units	1.1(0-3) units	P<0.001
Cryoprecipitate	4(1-6) units	0.5(0-2)units	P<0.001
Packed red blood cells	4(2-8)units	1(0-3)units	P<0.001

* Values are expressed as median and interquartile range.

** P value is considered significant if < 0.005.

Table III: Coagulation profile before and after rf VIIa

Item	Pre rf VIIa ^{(a)**}	Post rf VIIa ^{(b)***}	P value ****
*INR	1.6(1.1-2.3)	0.9(0.9-1.0)	P<0.001
*APTT(s)	49(36-60)	37(35-50)	P=0.008
Platelets (X 10 ⁹ /L)	140(90-170)	156(45-210)	P=0.85
*ACT(s)	150(110-165)	135(90-140)	P=0.836

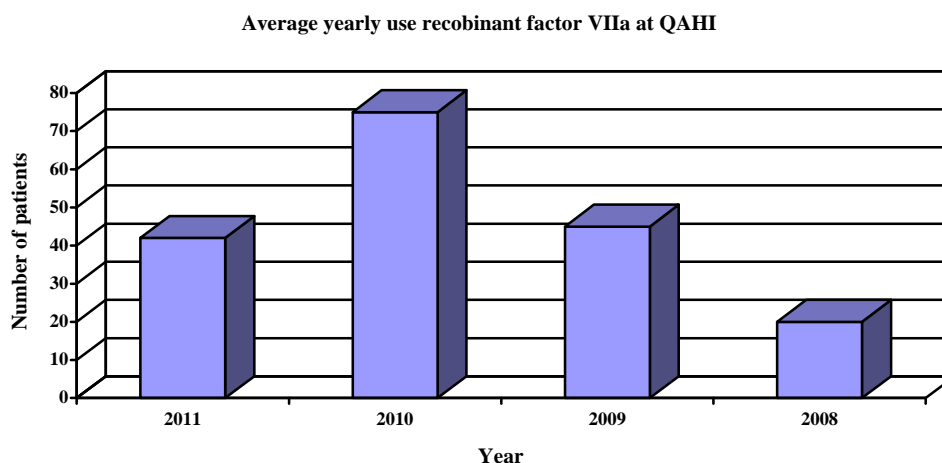
*INR (International Normalized Ratio), * APTT (Activated Partial Thromboplastin Time), *ACT (Activated Clotting Time), S (seconds).

** a: Coagulation profile before rf VIIa administration but after transfusion of blood products

*** b: Coagulation profile after administration rf VIIa .

(** a, *** b): values are expressed as median and interquartile range.

**** P value is considered significant if < 0.005.

**Fig 2:** Yearly use of recombinant factor VIIa at QAHI

disease and carotid stenosis but he was operated on emergency basis.

One patient had sternal wound dehiscence after he was opened 2 times (hemodynamically unstable) before Novoseven was given.

Two patients had postoperative strokes where this outcome was relatively expected as the first case was known to have previous recurrent events of Transient Ischemic Attack (TIA) and the second one underwent prolonged deep hypothermic circulatory arrest resulting in multiple ischemic brain injuries.

Three patients developed acute renal impairment where they were managed conservatively and had complete recovery.

The use of Novoseven showed no thromboembolic complications in our study group. The median ICU stay for patients received Novoseven comparing to nonbleeding group was 4 days (range 2-8 days) vs 1 day (range 1-3 days) and median hospital length of stay was 9 days (range 7-19 days) vs 6 days (range 5-8 days) respectively.

Discussion

Bleeding due to a non surgical cause is usually due to failure of the hemostatic pathways. The surgical trauma and use of cardiopulmonary bypass where the contact between the circuits of the pump and blood may result in hemodilution, activation of the fibrinolysis, hypothermia, and consumption coagulopathy.^(19,20)

Massive blood transfusion is a common topic in cardiac surgery where serious post operative complications such as adult respiratory distress syndrome, renal failure, sepsis, transfusion reaction and even death may occur.⁽²¹⁻²³⁾

It was suggested that when thromboelastography is performed during cardiopulmonary bypass and added to the current on hand model, excessive blood loss risk stratification is significantly improved.⁽²⁴⁾

In our study, it is clear that the use of rf VIIa was of great benefit in the management of life threatening bleeding after cardiac surgery. The cessation of blood loss, decline in the amount of the transfused blood and its products, normalization of the hematological parameters, fewer reoperation and absence of the common side effects proved its efficacy in practice.

The mean dose of the received Novoseven was 65µg/kg where 95 % of our study group received a single dose that was effective. It is still unclear what is the optimum dose used in cardiac surgery as doses ranging from 13-192 µg/kg yielded a satisfactory coagulation.⁽⁶⁾

While some studies showed the efficacy of using small dose of rf VIIa in the management of intractable bleeding,^(16,25-27) others raise the issue if there is any benefit ever over the conventional hemostatic therapy.^(28,29)

Around 84% of the patients received their dose in the intensive care unit where we so much support the idea that recombinant factor VIIa administration in the ICU (after exclusion of the surgical causes) appears sometimes comparable with the reopening for refractory bleeding after complex cardiovascular surgical procedures which might be in some patients another option substituting reoperation.⁽³⁰⁾

As Novoseven appears to be a safe and effective agent in controlling bleeding still there are some critics about the cost, time of administration, optimal dose and thromboembolic complications.⁽³⁾ It was suggested that the action of rfVIIa is so much suppressed by the hypothermia and acidosis;^(11,31,32) that's why we used to correct the temperature and metabolic status before commencement of management

Some groups support the idea of giving rFVIIa early in the course of refractory blood loss where the presence of adequate amount of circulating coagulation factors is much enough to ensure adequate hemostasis.^(33,34,35)

None of our patients developed thrombosis during Novoseven administration. The cause of the phenomena is theoretically attributed to the binding of the exogenous Factor VIIa to the tissue factor at the sites of vascular injury and the new couple allows conversion of Factor VII to VIIa which activate factor IX and X and enhance thrombin formation.

While some centers found no difference in the thromboembolic phenomena for patients received the Novoseven,^(3,36) others reported rates of 5.3%⁽³⁷⁾ and even in a very recent study it may reach up to 30% which might result in high mortality and morbidity.^(38,39)

Despite the fact that it is still not clear how much the influence of Factor VIIa on graft patency after coronary artery bypass grafting,^(16,40) a new study published recently by Levi et al suggested 2.5 times increase in the rate of coronary occlusion in comparison to placebo.⁽⁴¹⁾ A dose dependent effect was suggested for the thrombosis process in fresh vascular grafts occlusion in a rabbit model.⁽⁴²⁾

Although the incidence of reopening for bleeding in our center was about 4.5% which is very much comparable to what mentioned in the literature,⁽⁴³⁻⁴⁵⁾ still we agree with others opinion⁽⁴⁶⁻⁴⁸⁾ that more than 90% of the in-hospital use of rfVIIa were off-label. It

was the expensive cost beside the high rate of the off-label use that forced many institutions including our unit to develop their own guidelines to minimize the wasting of such a valued drug.

In order to give out a final comprehensive assessment regarding the cost-effectiveness, safety and proper use of recombinant factor VIIa, further analytical studies on a larger number of patients are needed.⁽⁴⁹⁾

Conclusion

It was clear from our experience that the use of recombinant factor VIIa was of great benefit in the management of life threatening bleeding conditions after cardiac surgery. It has the ability to control blood loss, restore hemostasis and decrease the amount of blood transfusion. In order to achieve the maximum benefit of Novoseven therapy and certainly after rolling out the surgical cause it should be administered early in the course of refractory bleeding after the correction of hypothermia and metabolic acidosis to ensure adequate environment for hemostasis.

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