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Recombining activated factor VII in cardiac surgery; case report and review of the scientific evidence

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SUMMARY

Introduction: Bleeding is a common complication in cardiovascular surgery with cardiopulmonary bypass. Conventional management is with blood products, antifibrinolitic drugs and surgical re-intervention, which is associated with high morbidity and mortality rates. **Objective:** To describe a case of intractable postoperative hemorrhage secondary to coronary revascularization successfully managed with Recombinant Activated Factor VIIa (rFVIIa) and review the literature about the use, security and safety of rFVIIa in cardiac surgery. **Case report:** A 56 year old man developed hemorrhage in the post-operatory period after coronary revascularization. He was refractory to management with fresh frozen plasma, cryoprecipitate, aprotinin, heparin reversion and rewarming, with successful response to two rFVIIa doses of 90 µg/kg each. There were no thromboembolic complications. Comment rFVIIa use in severe bleeding associated with cardiac surgery, controls and reduces hemorrhage, blood product requirements and the need for re-intervention. Dose varies from 30-60 µg/kg in pediatric patients and 90-100 µg/kg in adults in one or two applications. Its margin of safety is satisfactory with low incidence of thromboembolic complications. **Conclusion:** rFVIIa is an effective therapeutic alternative for both pediatric and adult patients with intractable bleeding after cardiac surgery.

Key words: Recombinant activated factor VII (rFVIIa), hemorrhage, cardiac surgery, coronary artery Bypass.

RESUMEN

Introducción: *La hemorragia es una complicación frecuente en el postoperatorio de procedimientos quirúrgicos cardiovasculares que requieren derivación cardiopulmonar. El manejo habitual es con productos sanguíneos, antifibrinolíticos y reexploración quirúrgica, esta última asociada a una elevada morbi-mortalidad y costos.* ***Objetivo:*** *Reportar un caso de hemorragia en el postoperatorio de revascularización coronaria refractaria al manejo habitual que respondió al Factor VII recombinante activado (FVIIra) y revisar la evidencia científica sobre el uso y seguridad del FVIIra en cirugía cardíaca.* ***Caso clínico:*** *Paciente de 56 años que presentó en el postoperatorio de revascularización coronaria hemorragia microvascular refractaria al manejo con plasma fresco, crioprecipitados, aprotinina, reversión de heparina y recalentamiento que respondió de manera satisfactoria a dos dosis de FVIIra de 90 µg/kg cada una. No se presentaron complicaciones tromboembólicas.* ***Discusión:*** *Varios estudios han demostrado que el uso de FVIIra en la hemorragia grave asociada a cirugía cardíaca controla y reduce la hemorragia, los requerimientos de*

productos sanguíneos y la necesidad de reintervención. La dosis varía de 30-60 µg/kg en niños a 90-100 µg/kg en adultos en una o dos aplicaciones. Su margen de seguridad es satisfactorio, con una baja incidencia de complicaciones tromboembólicas. ***Conclusión:*** *La terapia con Factor VII recombinante activado (FVIIra) se ha posicionado como una alternativa terapéutica efectiva para los pacientes adultos y pediátricos que presentan hemorragia refractaria al manejo habitual en el postoperatorio de cirugía cardíaca.*

Palabras clave: *Factor VII recombinante activado (FVIIra), hemorragia, cirugía cardíaca, revascularización coronaria.*

Post-surgical bleeding is one of the main complications of cardiopulmonary bypass (CPB) in patients undergoing cardiothoracic surgical procedures. The incidence of post-surgical bleeding ranges from 4% to 32%. The therapeutic strategies for this complication include administration of blood products, antifibrinolytics, protamine, control of acidosis, hypothermia and surgical re-exploration. From 3% to 5% of patients will need surgical reexploration, which is associated with high morbidity and mortality secondary to sepsis, renal failure, atrial arrhythmias and prolonged mechanical ventilatory support[1-3].

The recombinant activated Factor VII (rFVIIa) was introduced to clinical practice to manage hemorrhage in patients with Hemophilia type A and type B, who were treated with inhibitors. The first report, published in 1988, describes the effectiveness of rFVIIa in a patient with hemophilia type A, who underwent open knee synovectomy. After this first report, its clinical use was diversified for different purposes, such as treatment for acute hemorrhage or for prophylaxis against hemorrhage in patients taking inhibitors.

The rFVIIa is also indicated in patients that take clopidogrel, have aspirin-induced platelet dysfunction, Glanzmann thrombasthenia and Bernard-Soulier Syndrome. The current indications of rFVIIa are trauma; hepatic transplant; reversion of oral anticoagulants; major orthopedic surgery; hemorrhagic pancreatitis; cerebral, digestive and obstetric hemorrhage and cardiac surgery. Scientific evidence has shown that use of rFVIIa in the above mentioned situations, serves to control and decrease hemorrhage, improve results of tests for coagulation and reduce significantly the requirements for hemoderivatives with a high margin of safety[4-6].

The experience in Mexico to manage post-cardiac surgery hemorrhage with rFVIIa is scarce and there are few international publications that include a reduced number of patients. This paper has to objectives. First, to report a clinical case that treated with rFVIIa due to severe hemorrhage during the postoperative stage of coronary revascularization; second, to review the scientific evidence related to the use and safety of rFVIIa in cardiac surgery.

CLINICAL CASE

A 56 years-old, male patient with history of hypertension, heavy smoking, diabetes mellitus, sleep apnea and secondary polycythemia, was hospitalized due to clinical symptoms that had been present for a month. He had pain in the anterior chest region that was intense, oppressive and irradiated to the left arm. Moderate efforts triggered the pain that was present even when the patient was inactive. Clinical diagnosis of ischemic cardiopathy was established and following clinical studies were performed: electrocardiogram (ECG) in which repolarization diffuse abnormalities in the diaphragmatic wall and in the left ventricle anterior wall, were observed. The myocardial gammagram was positive for left ventricle ischemia. The echocardiogram showed thickening and calcification of the root and the aortic valve without evidence of stenosis or insufficiency; left ventricular hypertrophy, normal mobility, expulsion fraction of 61% and type I diastolic dysfunction. The coronariography showed the trunk without significant abnormalities, left anterior descending with obstruction of 90% before the first septal and 90% after the first diagonal. First diagonal with lesion of 90%, circumflex artery with proximal obstruction of 90%, left (obtuse) marginal artery with lesion of 100%; right coronary artery with significant lesions in the bifurcation of right (acute) marginal artery and posterior descending artery.

The treatment began with aspirin and clopidogrel (both were interrupted in the preoperative period) and coronary revascularization was programmed. During the transoperative period, coagulation tests, hemoglobin and platelets measurement showed following results: hemoglobin: 18.2 gm/dL; platelet count: 148,000/mL; prothrombin time (PT): 19.1 seconds with International normalized ratio (INR): 1.55; partial thromboplastin time (PTT): 46 seconds.

In the transoperative period, three aortocoronary bypasses were performed: internal mammary artery to anterior descendant, saphenous vein to posterior descendant, saphenous vein to intermediate branch. The aortic cross-clamp lasted 56 minutes and the cardiopulmonary bypass lasted 70 minutes; bleeding during this period was 600 mL; thus,

one unit of erythrocyte concentrate and three units of frozen plasma were transfused to the patient. Heparin was reversed 1:1 with protamine (5 mg/kg). The diuresis was 500 ml and Hartman solution was administered; therefore a positive balance of 720 mL was attained. It was necessary to administer nitroglycerin, dobutamine and levosimendan when the cardiopulmonary bypass was retired. so, an adequate hemodynamic function was obtained.

The patient was shifted to the intensive care unit with metabolic acidosis and hypothermia (350C). In mediastinal catheters he had drainage of fresh blood that did not coagulate. During the first 20 minutes, the output was 700 mL, hemoglobin was 14.1 g/dL; coagulation time and platelet count, were PT: 9.4 seg. INR: 0.76, PTT: 31.6 seg. Despite the treatment with platelet apheresis, fresh frozen plasma, protamine sulfate (1 mg/kg), correction of metabolic acidosis and aggressive external warming up, the hemorrhage persisted through the drainage tubes. The output was 100 mL in 20 minutes, to make a total of 800 mL in 40 minutes. Hence, it was decided to use recombinant activated Factor VII in a dose of 90 µ/kg. In the next 15 min, the hemorrhage was reduced to 50 mL. Later, a second dose of 90 µ/kg was applied. That allowed to control the bleeding and blood clots were observable in the drainage tubes along with 50 mL of serous-sanguineous fluid (Figure 1). Table I shows the progress of hemoglobin, platelets and coagulation times.

Due to the suspicion of obstruction of the mediastinal drainage tubes that would hide mediastinal hemorrhage, the patient was re-operated. The surgical findings during the second surgery were: scarce micro-vascular hemorrhage that did not require treatment and permeable bypasses without evidence of leakage. The patency of the bypasses was evident due to the absence of cardiac ischemia or myocardial infarction during the transoperative and postoperative periods. The echocardiogram showed good contraction of the left ventricle, the ejection fraction was 70%. The post-surgical progress was satisfactory. There was scarce drainage of serous-sanguineous fluid through the mediastinal drainage tubes. Extubation of the patient was in 24 hr although he developed left lung athelectasia that was solved by using physiotherapy and Bi-level Positive Airway Pressure (Bi-PAP). The patient was discharged from the intensive care unit. During the hospital follow-up, he did not show clinical evidence of coronary bypasses obstruction, venous thrombosis or deep venous thrombosis in lower limbs neither pulmonary embolism.

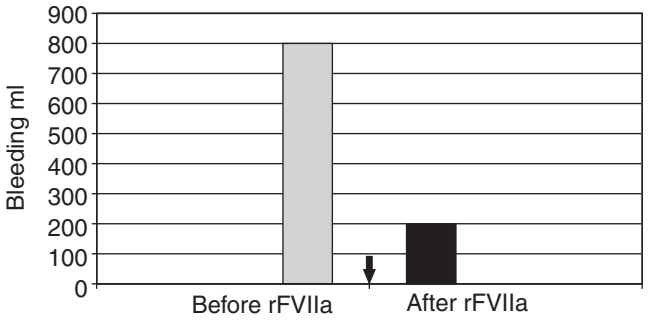

Figure 1. Amount of bleeding, before and after administering rFVIIa.

DISCUSSION

Hemorrhage that occurs during the transoperative period of cardiac surgery with cardiopulmonary bypass is classified as surgical and non-surgical. Surgical hemorrhage is related to the technique and is controlled surgically. Non-surgical hemorrhage is more severe and is secondary to a number of circumstances such as: preoperatory antiplatelet therapy, heparinization of the system and contact of the blood with artificial surfaces. This cause dysfunction of the hemostatic system, dilution and consumption of coagulation factors, hypothermia, acidosis and hyperfibrinolysis. Hypothermia has a deleterious effect on hemostasia because it delays the

Table I. hemoglobin, platelets, coagulation times, D-dimer, fibrinogen, Ivy bleeding time.

		Surgical period				
		Postoperative (hours)				
Tests	Preoperative	1	8	24	48	72
Hemoglobin (g/dL)	18.2	14.1	15	13.9	12.5	12.4
Platelets (10^3/mL)	148	163	127	171	146	129
PT (seg.)	19.1	9.4	9.2	13.2	12	12
PTT (seg.)	46	31.6	26.3	26.8	25	25.4
D-Dimer (ng/dL)		2.226				
Fibrinogen (mg/dL)	240	145	280	300	300	350
Ivy bleeding time (min)		19	10	5	5	

activation of coagulation factors and platelet aggregation. Acidosis interferes with the activation of enzymatic complexes on lipid surfaces. Non surgical hemorrhage is micro vascular (in layers) and persists despite of medical treatment and use of hemoderivatives. Most of these patients undergo surgical reexploration that causes further decline of hemostasia and increases significantly, hemorrhage, morbidity, mortality and costs of care[7-12].

Conventional management of hemorrhage after cardiac surgery includes blood products and antifibrinolytic drugs. Blood products are used to treat anemia and coagulopathy. Fresh plasma, cryoprecipitates and concentrates and/or platelet apheresis increase coagulation factors and the substratum for coagulation. Platelets are essential in patients that have severe thrombocytopenia or drug-related thrombocytopenia. However, administration of blood products has several drawbacks: high incidence of immune and non-immune reactions related with transfusion as well as potential of spreading diseases. This fact has prompted the development of several drugs with the pharmacological capability of promoting hemostasia, among which we can mention protamine, aprotinin, aminocaproic acid, tranexamic acid and desmopressin.

Protamine reverses the action of heparin, but it has several serious adverse effects such as hypotension, hypersensitivity reactions and paradoxical anticoagulation that happen with high doses of heparin. Aprotinin inhibits serine proteases with potent antifibrinolytic effect that can be administered as prophylaxis to avert hemorrhage complication in patients undergoing vascular surgery. However, routine prophylaxis is expensive and has been related to hypersensitivity reactions, mainly when several dosages have been applied. The aminocaproic acid and tranexamic acid are analogous of lysine; both bind to lysine receptors on plasminogen and exert its antifibrinolytic effect inhibiting the activation of plasminogen to plasmin. The effectiveness of these drugs is higher when administered during the preoperative period of cardiac surgery, than when administered during the postoperative period. Desmopressin increases release of Von Willebrand factor and of factor VIII from endothelial cells, which favor hemostasia. Despite of the above described mechanisms of action of these drugs, most have limited effect to control non-surgical hemorrhage during postoperative period[13-16].

The rFVIIa was originally developed to manage patients with hemophilia, but in the last years, it is being used for different circumstances associated with severe hemorrhage, among which is refractory hemorrhage during the postoperative period after cardiac surgery. In 2000, Aldoury et al reported the first case series of severe hemorrhage during the postoperative period after cardiac surgery that was treated with rFVIIa; the four cases had quick hemostasia improvement and a significant decrease of blood loss and of requirements of blood products. After such a study and until 2004, fourteen papers were published (case reports and case series) that comprised a total of twenty-eight pediatric and adult patients. The age interval of these patients ranged from twelve days to 75 years old and the surgeries were; heart valve replacement, arterial bypass, aortic aneurysm, atrioventricular canal, lung transplant, biventricular assist device support; coronary revascularization, interauricular communication repair. In 70% of cases, control of hemorrhage was satisfactory and was reached within the first hour. The dose of rFVIIa ranged from 30 - 120 µg/kg and the mean was 101µg/mL. On average 1.4 doses were required. The remaining 30% required two or three doses; the mean was 225 µg/kg. The bleeding was gradually stopped in these patients. In both groups, transfusion of hemoderivatives was significantly reduced and so was the need to reoperate (Table II)[17-31].

Based upon previous evidence and to validate efficacy and safety of rFVIIa, Von Heymann et al published in 2007 the results of a retrospective study in which a comparison between rFVIIa and conventional hemostatic treatment was carried out with twenty-four patients; those treated with rFVIIa had bigger blood losses that the control group and they required, before being treated, more transfusions (erythrocyte concentrates and fresh plasma elevated doses of aprotinin. Hemorrhage and transfusion requirements were reduced significantly after the administration of rFVIIa and no thromboembolic complications were present, but survival rates after six months were similar in both groups. According to the authors of the report, this last event can be related to the delay in the decision to using rFVIIa and to the fact that patients had worsened. An important contribution of this study is the new concept of the "ideal" time in which rFVIIa should be used. Previous studies had considered that rFVIIa as the last therapeutic alternative to be used when other resources had failed. After this study, the alternative of early use was established[32].

Karkouty et al published the largest study analyzing the effect of rFVIIa to control refractory hemorrhage after cardiac surgery. This study compared 114 patients treated with rFVIIa due to uncontrolled postoperative bleeding after cardiac surgery versus 541 patients not treated with rFVIIa. The results of this study corroborated what previous publications had reported, that rFVIIa reduces significantly hemorrhage and the requirements for blood products, without causing adverse effects, furthermore, emphasizes that early treatment is associated with better clinical progress[33].

In the years 2005 and 2006, several research groups published a number of studies in pediatric and adult patients. Besides of attaining similar results than previous studies these new studies validated that the rational and early use of rFVIIa reduces significantly the postoperative

Table II. Publications of recombining activated Factor VII in cardiac surgery (2000-2004).

Study/year	Age	Surgery	Dose of rFVIIa µ/kg	Results
Aldouri[17]/2000	25 years	Closing of interauricular communication and pulmonary artery repair	30	Quick hemostasia and correction of the coagulopathy in 1 hour; hemorrhage of 85 ml in four hours
	73 years	Mitral valve repair, tricuspid valve repair	30	Quick hemostasia and correction of the coagulopathy in 1 hour. The hemorrhage decreased from 900 mL to < 50 mL/h
	48 years	Mitral valve repair	30	Quick hemostasia and correction of the coagulopathy in 1 hour. The hemorrhage decreased from 300 mL to < 100 mL/h
	66 years	Aortic valve repair, aortic root replacement	30	Quick hemostasia and correction of the coagulopathy in 1 hour. The hemorrhage decreased to < 70 mL/h
	48 years	Mitral valve repair, repairmen of right aorto-ventricular fistula	30	The hemorrhage decreased to 300 mL within the first hour of postoperative and ceased after four hours. Quick correction of coagulopathy at 30 minutes
Hendriks[18]/2001	66 years	Repairmen of mitral and tricuspid valves,	90	Quick hemostasia and correction of the coagulopathy
Potapov[19]/2002	57 years	Assisted biventricular device	120 x 1 60 x 1	Hemorrhage decreased from 1 Lt/h to 500 mL/h after the first dose of rFVIIa; the hemorrhage decreased to < 100 mL/h, two hours after administering the second dose of rFVIIa, allowing to close the thorax
Von Heymann[20]/2002	65 years	Repair of cardiopulmonary bypass	50 x 2	The drainage in mediastinal catheters decreased 50% after the first dose of rFVII decreased to 40 mL immediately after the second dose
Kastrup[21]/2002	26 years	Aortic valve replacement	40	Quick hemostasia, high levels of cardiac enzymes in the first postoperative day, emergency cardiac catheterism; no cardiac disease was identified. The patient was discharged from the intensive care unit after 2 days of postoperative period
Bui[22]/2002	56 years	Pulmonary transplant, cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO)	90 x 1 55 x 1	Gradual hemostasia after each dose of rFVIIa; hemorrhage persisted in 300 mL/h. Administration of prothrombin activator complex (PAC). Several minutes after administering PAC the patient suffered cardiogenic shock. Bleeding stopped after 20 min., after suspecting intracardiac massive thrombosis and extracorporeal oxygen
Naik[23]	75 years	Bioprosthetic replacement of aortic valve, supra-coronary ascending aorta replacement	107	Hemorrhage decreased from 400-500 mL in 11 hours to 40 mL/h
Tanaka[24]/2003	74 years	Mitral valve replacement, Jehovah witness	45	Quick hemostasia and correction of the coagulopathy, allowing thorax closing; postoperative hemorrhage 200 mL in 4 hours, 740 mL in 24 hours. The patient required prolonged respiratory support
	49 years	Mitral valve replacement, Jehovah witness	60	Quick hemostasia in 3 min. Thorax closing, postoperative hemorrhage 270 mL, since the patient was admitted to the intensive care unit, hemorrhage decreased to 55 mL/h; total 1090 mL/24 hr. Patient was discharged from the ICU after 4 days of postoperative

Study/year	Age	Surgery	Dose of rFVIIa μ/kg	Results
Tobias[25]/2003	4 months	Interauricular communication	70	Quick hemostasia and correction of the coagulopathy. rFVIIa at day 7 of postoperative period to correct recurrent coagulopathy, and to remove the catheter of the transthoracic pulmonary artery. The patient was discharged on day 21 of postoperative period
Leibovitch[26]/ 2003	10 weeks	Repair of the atrioventricular septal defect	100 x 4	It was reached gradual hemostasia; additional blood products were not required. The patient was discharged from ICU 4 days after surgery and from the hospital 7 days after surgery
Wahlgren and Swedeborg[27]/ 2003	62 years	Abdominal aortic aneurysm repair	80	Quick hemostasia, after slow progress during hospital say, the patient began to rehabilitate
Lucey[28]/ 2003	15 years	Bilateral pulmonary transplant	Non available	Quick hemostasia, development of cardiac tamponade associated to mediastinal thrombosis that required surgical evacuation
Verrijckt[29]/ 2004	12 days	Ligature of the patent ductus arteriosus; closing of atrioventricular septal defect	30	Quick hemostasia and correction of the coagulopathy. Death at 11 days of postoperative period due to persistent cardiac failure
DiDomenico[30]/ 2004	51 years	Repair of thoracoabdominal aneurysm	120	Quick hemostasia and correction of the coagulopathy
	28 years	Replacement of mitral valve, replacement of aortic valve, aortic root repair, reinsertion of coronary arteries	100 x 3 doses	Gradual hemostasia, hemorrhage gradually decreased after initiating the prothrombin activating complex and third dose of rFVIIa. The patient was discharged after 18 days of postoperative period without complications
Pychinska[31]/ 2004	8 pediatric patients	Congenital cardiopathy	30	Control of hemorrhage, no reoperation

hemorrhage after cardiac surgery, the requirements of blood products and the need of reoperation, without deleterious effects (Table III)[33-39].

The ideal dose of rFVIIa has not yet been established. According to data obtained from the literature review, the recommended dose for adults is 90-120 μ/kg and for children is 30-60 μ/kg. In most cases, one dose is enough and if a second dose is required, it should be applied within 30 minutes. There is no proof that using more than two doses will increase the effectiveness of rFVIIa.

The rFVIIa promotes hemostasia through increasing the production of thrombin in the platelet surface which is the basis of the coagulation cellular model. According to this model, the process of hemostasia occurs on a cellular surface and the trigger is the complex FVIIa/Tissue factor (TF). Its fundamental components are:

1. Tissue factor
2. Activated platelets
3. Endothelial cells
4. Control mechanisms

The tissue factor is a membrane protein that is expressed in extravascular cells that surround blood vessels (fibroblasts, smooth muscle cells) endothelium and leucocytes. This is the only coagulation factor that is not in the blood and its synthesis is under transcription control which is triggered as a response to trauma, inflammation and hormone products. Once TF is expressed, it binds to Factor VII to integrate the complex FVIIa/TF. This complex links to the cell surface and activates factors IX and X. Activated platelets are the template in which cofactors VIIIa and Xa and its enzymes (Factor IXa and Xa) bind in such a way that assembles the prothrombinase complex.

The endothelial lesion exposes great amounts of tissue factor to the circulation that along with platelet activation it induces the thrombin activation. Antithrombin inhibits the excess of thrombin in a process that occurs in the surface

of endothelial cells when thrombomodulin is activated. Thrombomodulin-bound thrombin (TT complex) induces the activation of protein C that, in presence of inactive protein S, inactivates factors Va and VIIIa. In this way, formation of thrombin and the blood clot are located in the zone of endothelial damage.

The mechanisms controlling the coagulation process are: the tissue factor pathway inhibitor; protein C; antithrombin and glucosaminoglycans of the vascular wall. The new cellular model of hemostasia complements the traditional model in which the role of the cells was exclusively to offer a carrier surface for phosphatidylserine, which is useful to assemble procoagulant complexes. According to this model, hemostasia development occurs in three simultaneous stages on different cellular surfaces. The first or initiation occurs in carrier cells of the tissue factor (endothelium, subendothelium); at the second or amplification, the system prepares itself to produce thrombin at a great scale and at the third stage or propagation occurs on the platelet surface[40-50].

The main complication associated to rFVIIa is thrombosis. It has been reported cases of deep venous thrombosis, pulmonary embolism, brain infarction, myocardial infarction in patients treated with rFVIIa. Global incidence of thromboembolism associated to rFVIIa is 1.4%. In cases of thrombosis associated to rFVIIa several risk factors were present, thus, it is recommended its cautious use in patients with sepsis and when there are unstable atherosclerotic plaques due to the elevated expression of the tissue factor, which increases the risk for thrombotic events.

Several authors have proposed that the hemorrhage in the postoperative stage after cardiothoracic surgery associated with disseminated intravascular coagulation can increase the thromboembolic risk if rFVIIa is used. That was reported in two patients during the postoperative period after lung transplant. According to current evidence, the risk for thromboembolic complications associated with rFVIIa in patients undergoing cardiothoracic surgery is low and the safety profile is satisfactory[51-54].

The cost is a major limitation to use rFVIIa in our milieu. Every milligram costs about US$1,000. However, if we take into account the high costs and adverse effects associated with the transfusion of blood products and with the surgical reexploration to manage hemorrhagic complications, it seems that administration of rFVIIa is cost-effective in selected cases or in special groups of patients that reject transfusions, such as Jehovah witnesses[24].

Non-surgical severe hemorrhage was the main problem of our clinical case. The hemorrhage did not compromise with tissue oxygenation due to the fact that the patient had a pulmonary disease with secondary polyglobulia. (Hemoglobin 18 g/dL); besides, during the transoperative period, the patient was transfused with a concentrate of eryth-

Table III. Publications of recombining activated Factor VII in cardiac surgery (2005-2006).

Author/year	Number of patients	Surgery	Dose of rFVIIa µ/kg	Results
Hyllner[34] 2005	24 patients	CPB	77.5	15 patients were reoperated, 5 patients reoperated twice; after the second dose of rFVIIa, the hemorrhage decreased from 450 ml to 250 mL
Halkos[35] 2005	9 patients	CPB, MVR, AAA repair	94	Decrease of the hemorrhage from 640 mL to 100 mL. Any patient required surgical re-exploration after the administration of rFVIIa
Razon[36] 2005	5 pediatric patients	Cardiac surgery	30	Significant decrease of hemorrhage
Farzan[38] 2006	17 (65 to 73 years of age)	CPB, coronary artery. MVR, TVR AAA repair	125.55	Control of hemorrhage
Ekert[37] 2006	40 patients (< 1 year)	CPB	40	Control of hemorrhage
Karkouti[33] 2006	114	Cardiac surgery	30-60	Control of hemorrhage
Romagnoli[39] 2006	15	Cardiac surgery	12	Control of hemorrhage

AAA = Abdominal aortic aneurysm; CPB = Cardiopulmonary bypass; MVR = Mitral valve replacement; TVR = Tricuspid valve replacement.

rocytes, which served to maintain his levels of hemoglobin in 12 g/dL on average. This fact disregarded the heparin anticoagulant effect; despite of the fact that it was decided to apply a new dose of protamine that did not have any effect at all.

The low levels of fibrinogen were secondary to hyperfibrinolysis and were corrected quickly after using rFVIIa. The platelet account was within the hemostatic range, despite the evidence that these were malfunctioning. This was proved by a bleeding time of 19 minutes. We interpret that this malfunctioning has a multi-causal etiology associated with acidosis, hypothermia and the effect of aspirin and clopidogrel that the patient had received in the preoperative period, and it was not suspended at the recommended time.

The treatment was according to scientific evidence. First, acidosis and hypothermia were controlled; then, the treatment continued with blood products, mainly fresh plasma and platelet apheresis, this was because the patient received platelet antiaggregant medication before the surgical procedure. He had an inadequate response to the treatment and after correcting the acidosis and hypothermia, we decided to administer early rFVIIa. The patient received two doses of 90 μmg/kg, each. This treatment decreased significantly the hemorrhage and the transfusion requirements, such as is depicted in figures 1 and 2.

The patient was re-explored not due to the hemorrhage, but because of the suspicion that blood clots were obstructing the drainage tubes, thus masking the hemorrhage. During the surgery we corroborated proper hemostasia and permeability of the coronary bypasses. There were not thromboembolic complications (deep venous thrombosis, pulmonary thromboembolism or vascular access thrombosis) associated with the use of rFVIIa. The response that we observed corroborated the importance of providing integral care to this complication and the profile of safety and efficacy that rFVIIa has for the early treatment of non-surgical hemorrhage during the postoperative period of cardiac surgery[55,56].

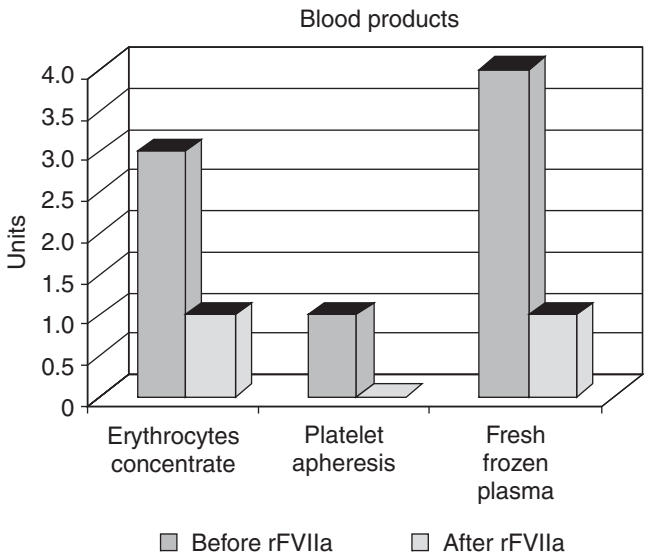

Figure 2. Requirement of hemoderivatives before and after administering rFVIIa.

According to the reviewed scientific evidence, we can conclude that rFVIIa is useful for the management of non-surgical hemorrhage during the postoperative period of cardiac surgery when other conventional measures have failed. Published studies have proved that with an adequate safety profile, rFVIIa reduces significantly hemorrhage, transfusional requirements and the need to reoperate; it is advisable to use it early, after correcting hypothermia, acidosis and platelet account. Further studies including a bigger number of patients are required to corroborate current evidence.

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