

Recombinant factor VIIa (NovoSeven[®]) as a hemostatic agent after surgery for congenital heart disease

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Summary

Background: Postoperative bleeding and blood product requirements can be substantial in children undergoing open-heart surgery, and reexploration is required in 1% of cases. Recombinant activated factor VII (rFVIIa, NovoSeven[®], NovoNordisk, Denmark) is a hemostatic agent approved for the treatment of hemophilic patients with inhibitors to factor VIII or factor IX. It has also been used with success in other conditions. We present our experience with rFVIIa treatment for uncontrolled bleeding after open-heart surgery in five pediatric patients.

Methods: The study group consisted of five patients after open-heart surgery with excessive blood loss. The patients were treated with rFVIIa after failure of conventional treatment to control the bleeding. Blood loss, blood product consumption, and coagulation test results were recorded before and after rFVIIa administration.

Results: In all cases, blood loss decreased considerably after rFVIIa administration (mean 7.8 ml·kg⁻¹·h⁻¹), almost eliminating the need for additional blood products, and the prolonged prothrombin time normalized. In two patients with thrombocytopenia, rFVIIa helped to discriminate surgical bleeding from bleeding caused by a defect in hemostasis. No side effects of rFVIIa treatment were noted.

Conclusions: These cases support the impression that rFVIIa is efficient and safe in correcting hemostasis in children after cardiopulmonary bypass when other means fail. However, the data are still limited, and more extensive research is needed.

Keywords: cardiopulmonary bypass; congenital heart disease; recombinant factor VIIa; postoperative bleeding

Introduction

Postoperative bleeding and blood product requirements can be substantial in children undergoing open-heart surgery, reaching 15–110 ml·kg⁻¹ (1), and reexploration is required in 1% of cases (2,3). Bleeding after cardiopulmonary bypass (CPB) is caused mainly by a disturbance in hemostasis induced by the reduction in fibrinogen and coagulation factor activity, thrombocytopenia, and abnormalities in platelet function, complement activation, or fibrinolysis. Neonates and infants are particularly susceptible because of their characteristically increased inflammatory response to CPB and variable response to heparin, in addition to their low levels of coagulation factors (II, V, VII, X, XI and XII) before 6 months of age and prolonged activated partial thromboplastin time (PTT) before 3 months of age. Other risk factors in the pediatric age group include dilution coagulopathy (high ratio of CPB volume to blood volume) and cyanotic heart disease leading to thrombocytopenia and thrombocytopenia (2,4). The agents used to decrease blood loss and lower the need for allogeneic blood transfusion include plasma products and platelets, as well as drugs such as aprotinin, aminocaproic acid, and tranexamic acid, and recombinant coagulation products (4,5).

Recombinant activated factor VII (rFVIIa, NovoSeven[®], NovoNordisk, Denmark) is a hemostatic agent approved for the treatment of hemophilic patients with inhibitors to factor VIII or factor IX. It has also been used with success in other conditions (6). The aim of the study was to describe our experience with the postoperative use of rFVIIa in five children after open-heart surgery.

Methods

In 2002, 325 patients were hospitalized in the pediatric cardiac intensive care unit (CICU) after open-heart surgery. Five had excessive blood loss and were treated with rFVIIa on a compassionate-use basis, after oral consent was provided by the parents. Excessive blood loss was defined as more than 4 ml·kg⁻¹·h⁻¹ for three consecutive hours or more than 8 ml·kg⁻¹·h⁻¹ for any time period. Blood products were given according to our departmental protocol: fresh frozen plasma (FFP) 15–20 ml·kg⁻¹ (one unit in adults); platelets 1 unit·10 kg⁻¹,

cryoprecipitate (in cases of fibrinogen less than 100 mg·dl⁻¹) 1 unit·5 kg⁻¹. If two infusions of blood products did not attenuate bleeding, then rFVIIa was administered at a dose of 90 µg·kg⁻¹, as recommended for hemophilic patients (7,8). Actual doses ranged from 56 to 96 µg·kg⁻¹ (mean 80 µg·kg⁻¹) because of imprecise weight calculations or physician reluctance to open another vial of NovoSeven[®], owing to its high cost. rFVIIa was diluted with water and administered by bolus injection intravenously over a period of 2–5 min; NovoSeven[®] should not be mixed with infusion solution or be given in a drip, in accordance with the manufacturer's instructions.

Data on hematological values, amount of blood loss, blood product consumption, and coagulation tests before and after rFVIIa administration were collected retrospectively from the operative and CICU charts.

Results

The demographic data of the five patients are presented in Table 1. Age ranged from 3 days to 19 years. Two patients had thrombocytopenia with prolonged bleeding time (Ivy method). Both had had an extensive hematological workup before surgery, and except for undefined platelet dysfunction, their coagulation system was normal.

Table 2 shows the amount of blood loss from surgery to after rFVIIa administration. Blood loss was 4.5–21 ml·kg⁻¹·h⁻¹ (mean 9.8 ml·kg⁻¹·h⁻¹) before rFVIIa administration and decreased to 0.57–3 ml·kg⁻¹·h⁻¹ (mean 2 ml·kg⁻¹·h⁻¹) after. For patient 2, blood loss before rFVIIa administration could not be evaluated because the bleeding was from an open chest wound, and the chest drains were plugged.

The blood product requirement also decreased significantly after rFVIIa administration (Table 2). Patients 1 and 2 did not need any blood products after receiving rFVIIa. Patient 5 developed severe liver failure and therefore received FFP immediately after rFVIIa to compensate for the deficiency in other coagulation factors. The change in coagulation tests after rFVIIa administration is shown in Table 3. The prolonged prothrombin time (PT) noted before administration [international normalized ratio (INR) 2.07–5.87] reverted to normal (INR 0.54–1.34) in all cases. PTT was shortened in all patients, but did not always reach normal range.

Table 1
Demographic features of children treated with rFVIIa

Patient number	Sex	Age	Weight (kg)	Heart disease	Surgery	Hemostatic defect	Abnormal coagulation tests before surgery
1	M	18.5 years	71	TOF after repair, dilated right ventricle, free pulmonary insufficiency	Pulmonary homograft		
2	M	3 day	2.8	TGA, DILV, mitral atresia, pulmonary atresia	B-T shunt		
3	M	19 years	50	Pulmonary stenosis, Noonan syndrome	Pulmonary homograft	Thrombocytopathy	Bleeding time – 12 min
4	F	14 years	25	Pulmonary stenosis, previous ASD closure and pulmonary valvuloplasty Noonan syndrome	Pulmonary homograft	Thrombocytopathy	Bleeding time – 16 min
5	F	3.5 months	10.7	TOF	TOF repair		

TOF, tetralogy of Fallot; TGA, transposition of great arteries; DILV, double inlet left ventricle; ASD, atrial septal defect; B-T shunt, Blalock-Taussig shunt.

Table 2
Blood loss and blood product requirements from surgery to rFVIIa administration and 8 h after rFVIIa administration

Patient number	rFVIIa dose ($\mu\text{g}\cdot\text{kg}^{-1}$)	Time to rFVIIa administration (h)	Blood loss		PC		FFP		Platelets	
			Before ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)	After ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)	Before ($\text{ml}\cdot\text{kg}^{-1}$)	After ($\text{ml}\cdot\text{kg}^{-1}$)	Before ($\text{ml}\cdot\text{kg}^{-1}$)	After ($\text{ml}\cdot\text{kg}^{-1}$)	Before (units)	After (units)
1	84	5.5	5.7	0.57	21	0	11.2 (4 units)	0	12	0
2	78	7	21	2.5	217	0	92	17.8	16	0
3	56	7	4.5	2.8	20	5.6	20 (5 units)	0	12	0
4	96	2	8	1.44	30	0	16	8.4	12 SD	0
5	84	48		3	73.8	18	82	0	4	0

PC, packed cells; FFP, fresh frozen plasma; SD, single donor.

Table 3
Hematological values and coagulation tests before and after rFVIIa administration (blood samples were drawn less than hour before and after administration)

Patient number	Lowest hemoglobin ($\text{g}\cdot\text{dl}^{-1}$)	PT-INR		PTT (s)		Fibrinogen ($\text{mg}\cdot\text{dl}^{-1}$)		Platelets ($\times 10^9\text{l}^{-1}$)	
		Before	After	Before	After	Before	After	Before	After
1	7.6	2.34	0.54	45	41	193	257	221	192
2	11.7	5.87	1.04	120	50	101	172	136	151
3	10.7	2.07	0.58	43	35	262	316	237	219
4	11.8	2.18	0.57	69	49	386	413	130	147
5	8	2.69	1.34	33.7	27	208	194	71	40

PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time.

Discussion

Factor VIIa is a protein synthesized by the liver and plays a significant role in the coagulation process via its interaction with tissue factor (TF), the extrinsic

pathway. It is found on various types of cell in the deeper layers of the blood vessel wall. Hemostasis is initiated on exposure of TF to blood and the subsequent formation of TF-factor VIIa complexes on the TF-bearing cells. These complexes activate

factor X to factor Xa, leading to the conversion of prothrombin to thrombin. The limited amount of thrombin formed through this pathway generates a process that induces further factor X activation and full thrombin generation. This process seems to be compartmentalized and confined to the surface of thrombin-activated platelets and TF-bearing cells.

Evidence from the extensive use of rFVIIa in the hemophilic population demonstrates that rFVIIa enhances hemostasis at the site of injury, apparently without the systemic activation of the coagulation cascade (6,9). The modes of action of rFVIIa include both a TF-dependent mechanism and the generation of factor Xa and IXa on the surface of activated platelets by a mechanism unrelated to TF. The second mode requires a higher-than-normal plasma concentration of rFVIIa; hence the recommendation for the high dose of $90 \mu\text{g}\cdot\text{kg}^{-1}$ of rFVIIa in hemophilic patients (6,9).

RFVIIa has been proven effective in the treatment of severe bleeding episodes in hemophilic patients with inhibitors to factor VIII and IX or with factor VII deficiency. It has also been shown to have a hemostatic effect in thrombocytopenic patients and patients with thrombocytopathy (6,7). A hemostatic effect of rFVIIa has been described in a limited number of patients after massive tissue trauma caused by extensive surgery or injury (4,6,10).

This work describes five patients after open-heart surgery with CPB who had excessive bleeding and altered hemostasis. The use of CPB and hypothermia during surgery combined with other problems, such as congenital thrombocytopathy or liver failure, were the cause of the altered hemostasis. In all cases, initial attempts to achieve hemostasis with repeated blood product administration failed. Use of rFVIIa led to a significant reduction in bleeding and correction of coagulation. This response was similar to that reported by Al Douri *et al.* (11), Hendriks *et al.* (8) and Tobias *et al.* (12). Their publications include two pediatric patients. Al Douri *et al.* (11) described a 2.5 year old child who underwent arterial switch, closure of a Blalock–Taussig shunt and closure of an atrial septal defect. Blood loss during surgery was approximately 4.5 l, hemostasis was difficult to secure, and there was excessive oozing. Prior to the use of rFVIIa, the patient received 1 unit of FFP and 1 unit of platelets. RFVIIa was administered intraoperatively, at a dose of

$30 \mu\text{g}\cdot\text{kg}^{-1}$, and bleeding was reduced to 85 ml within 4 h postoperatively (about $2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$; weight was not documented). There were no serious side effects of treatment. The second reported pediatric patient was a 4-month-old after atrial septal defect repair (12). Persistent coagulopathy was noted during the immediate postoperative period with INR 6.8 and PTT 96.5 s; blood loss was about $10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. RFVIIa was administered at a dose of $70 \mu\text{g}\cdot\text{kg}^{-1}$ leading to a correction of INR to 0.8 and of PTT to 40 s, and a decrease in blood loss to $4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. Again, no significant adverse effects were noted. In the present study we used a mean dose of $80 \mu\text{g}\cdot\text{kg}^{-1}$ (Table 2), as recommended for hemophilic patients (7,12). However for the patients described by Al Douri *et al.* (11), a dose of $30 \mu\text{g}\cdot\text{kg}^{-1}$ was effective. The exact dose for patients after CPB has yet to be established.

Although all our patients received rFVIIa for uncontrolled bleeding after surgery, the causes of the bleeding were slightly different. Two patients (1 and 2) had a normal coagulation system before surgery and normal liver function at the time of bleeding. The excessive bleeding in these cases was attributed only to the alteration in hemostasis caused by the CPB and hypothermia: platelet abnormalities, complement activation, fibrinolysis, hemodilution (in the neonate), and inflammatory response (4). Patient 2 underwent re-sternotomy (before rFVIIa administration), but no bleeding source was found. The PT was not corrected by FFP. RFVIIa effectively stopped the bleeding, but the patient developed severe liver failure, severe capillary leak, and cardiac failure, and died 1 week after surgery.

Two other patients (3 and 4) had a known thrombocytopathy with prolonged bleeding time (Table 1). The hemostatic effect of rFVIIa in these cases is supported by the good results reported in other patients with functional platelet disorders, such as Bernard–Soulier syndrome and Glanzmann's thrombasthenia (6,13).

Thrombocytopenia and platelet dysfunction play a major role in postoperative bleeding after CPB. *In vitro* experiments demonstrated that thrombin generation by rFVIIa in the presence of factor VIII and IX (i.e. nonhemophilic state) was three to four times higher than in the hemophilic state. RFVIIa appears to significantly increase the cumulative amount of thrombin generated on the platelet

surface in individuals with an otherwise normal hemostatic state. Therefore, even in the presence of fewer functioning platelets at the site of injury, rFVIIa would be able to generate sufficiently high levels of thrombin to promote normal hemostasis (7). Patient 3 had massive bleeding that failed to stop with administration of FFP, platelets, and blood. We related the bleeding to the thrombocytopenia, and rFVIIa was given. Blood loss decreased considerably (Table 2) and the PT-INR was corrected (2.07–0.58). The continued blood loss in the presence of normal coagulation tests made surgical bleeding very likely. The patient underwent re-sternotomy, and bleeding from a suture line was detected and corrected. After surgery, the bleeding stopped (Table 2). Patient 4 received rFVIIa for massive bleeding that started in the operating room immediately after weaning from the CPB machine. She received FFP, platelets, and blood in the operating room and rFVIIa 2 h later. The blood loss decreased abruptly, from 8 to $1.44 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and PT normalized (Table 2). In the patients with thrombocytopenia, rFVIIa decreased or stopped the bleeding and helped us to discriminate surgical bleeding from bleeding caused by a hemostatic defect.

Patient 5 had persistent bleeding from an open chest wound. The rate of bleeding was difficult to assess because the chest tubes were plugged. She developed severe liver dysfunction combined with dilution coagulopathy caused by the recurrent blood product administration (Table 2). After treatment with rFVIIa, the bleeding slowed, so that the chest could be closed and new chest tubes placed. Blood loss was reduced to $3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, and PT normalized. However, PT again became abnormal 1 day later, and FFP was given repeatedly until recovery of liver function and hemostasis. Patients with liver failure have low levels of factor VII and other coagulation factors. rFVIIa has been shown to be effective in correcting PT in cirrhotic patients and in inducing hemostasis in patients with liver disease undergoing surgical procedures (14,15).

The interval between admission to the CICU and rFVIIa administration ranged from 2 to 48 h. For patients 1, 2 and 3, the interval was 5.5–7.0 h, because they were first given two to three courses of FFP, platelets, and cryoprecipitate (if needed) in an effort to achieve hemostasis and a sufficient level of coagulation factors for rFVIIa action. The interval

for patient 4 was shorter (2 h), because of the known thrombocytopenia and the administration of blood products in the operating room. Patient 5 had an extremely prolonged time to rFVIIa administration (48 h) because the exact volume of blood loss was difficult to assess. We believe the appropriate time is 5–7 h from admission, following treatment with two courses of blood products, as in patients 1, 2 and 3.

Some authors have raised concerns that rFVIIa administration after open-heart surgery may cause thrombotic events in patients with normal preoperative coagulation (16). Ischemic heart disease is rare in the pediatric population, making thrombotic events unlikely, though the risk is increased in children with prosthetic valves, aortopulmonary shunts, or atrial fibrillation, and in those with cavopulmonary anastomoses such as Fontan or bidirectional Glenn (4). In our series, only patient 2, who had a Blalock–Taussig shunt, was at risk of thrombosis. Neither our patients nor the other patients described in the literature (8,11,12) had thrombotic events. Other side effects of rFVIIa, such as fever, vomiting, changes in blood pressure, and dermatological reactions, were not documented in our patients or in the other patients described (8,11,12). A temporal relationship can be pointed out between rFVIIa administration and liver dysfunction in patients 2 and 5. In patient 2, the immediate postoperative period was characterized by a low cardiac output state and high inotropic support, followed by the development of multiorgan (including liver and renal) failure. The liver failure was most probably attributable to this course, and not to the rFVIIa administration. In patient 5, the liver failure developed before rFVIIa administration.

We describe five patients after open-heart surgery with CPB in whom excessive bleeding could not be controlled by blood products or exploration. When two courses of blood products failed to correct the coagulation (usually 5–6 h postoperatively), rFVIIa was administered. All patients showed a remarkable decrease in blood loss and correction of coagulation tests. No side effects of rFVIIa treatment were noted. Our results are similar to those reported in other pediatric patients and in adult patients in this setting. These cases support the impression that rFVIIa is efficient and safe in correcting hemostasis in children after CPB when other means fail. However,

the data are still limited, and more extensive research is needed.

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