

BRIEF REPORT

Management of Coagulopathy With Recombinant Factor VIIa in a Neonate With Echovirus Type 7

Jakica Tancabelic, MD* and Steven Edward Haun, MD

A 5-day-old newborn presented with neonatal enteroviral infection. The patient's hospital course was complicated by acute liver dysfunction, renal insufficiency, fluid overload, respiratory failure, hypertension, catheter related thrombosis, *Klebsiella pneumoniae* sepsis, intracerebral and intraventricular hemorrhage, and disseminated intravascular coagulation (DIC). Administration of fresh frozen plasma (FFP) and cryoprecipitate failed to control the patient's hemostasis and led to significant fluid overload. Recombinant activated factor VII (rFVIIa, Novoseven[®] NovoNordisk, Bagsvaerd,

Denmark) was given to the neonate as a bolus (rFVIIa at 60–80 µg/kg body weight), followed by a continuous infusion (2.5–16 µg/kg/hr). Recombinant activated factor VII controlled hemostasis, until the patient's liver function recovered. The patient's blood product requirement significantly decreased and his fluid overload resolved. Administration of rFVIIa appears to have stabilized the coagulation process. The patient appears to have fully recovered from the infection's complications. *Pediatr Blood Cancer* 2004;43:170–176. © 2004 Wiley-Liss, Inc.

Key words: coagulopathy; echovirus type 7; recombinant factor VIIa

INTRODUCTION

Severe disseminated enteroviral infection is commonly associated with echoviruses and occurs almost exclusively in neonates [1–3]. The initial nonspecific infection rapidly progresses to multisystem organ dysfunction characterized by DIC, jaundice, and liver failure. Severe bleeding episodes resulting from liver dysfunction are seen in newborns infected with echoviruses [4–6]. In such patients, hemostasis is difficult to achieve despite administration of FFP, cryoprecipitate, and other blood products. Often, infants develop symptoms of fluid overload due to the volume of FFP and cryoprecipitate administered. An increased consumption of platelet and coagulation proteins caused by DIC worsens the bleeding tendency. We describe the successful response to rFVIIa infusion in a newborn male infant with echovirus type 7 infection causing acute liver dysfunction, severe coagulopathy, persistent bleeding resulting in anemia, and intracranial hemorrhage despite the administration of FFP, cryoprecipitate, platelets, and packed red blood cells.

MATERIALS AND METHODS

Laboratory assays were carried out using standard methods. Viral cultures were done on a RMK cell line. The isolated enterovirus was serotyped with LBM pooled antisera (distributed by the World Health Organization). The viral isolation and serotyping were performed at the South Dakota Department of Health, Public Health Laboratory, Pierre, SD.

CASE REPORT

A male infant was born to a 27-year-old mother at 36 weeks gestation. Vaginal delivery was without complications. The birth weight was 2.3 kg and Apgar scores were 9 and 9 at 1 and 5 min, respectively. The mother was febrile at the time of delivery, with a history of cold symptoms lasting for a week. The infant was discharged home on the second day of life, and soon developed lethargy and poor suck resulting in inadequate oral intake. On the fourth day of life, the infant was admitted to the local hospital. The infant was hypothermic (34.6°C), thrombocytopenic (23,000/µl), hypoglycemic (36 mg/dl), and had episodes of periodic breathing. The patient was transferred to our institution for further management.

On arrival to the pediatric intensive care unit, the baby's vital signs were as follows: temperature 35°C, heart rate 144 beats/min, respiratory rate 36 breaths/min, and blood pressure 74/47 mm Hg. The infant was jaundiced, and

University of South Dakota School of Medicine, Department of Pediatrics, Pediatric Critical Care Medicine, Sioux Falls, South Dakota

The patient's care was provided at Sioux Valley Hospital and University of South Dakota Medical Center, Sioux Valley Children's, and Sioux Valley Children's Specialty Clinic, Sioux Falls, SD.

*Correspondence to: Jakica Tancabelic, University of South Dakota School of Medicine, Department of Pediatrics, Pediatric Hematology/Oncology, 1305 West 18th Street, Sioux Falls, SD 57117.

E-mail: jtancabe@usd.edu

Received 19 November 2003; Accepted 8 April 2004

petechiae were noted on the back and extremities. Examination of the patient's abdomen did not reveal hepatosplenomegaly. Blood and urine cultures were obtained as well as viral cultures of nose, throat, and rectum. TORCH titers were also sent. Throat and rectal swabs were ultimately positive for enterovirus. Typing of the enterovirus indicated echovirus type 7.

The patient was treated with supportive care including oxygen, warming, and intravenous fluids. He was empirically treated with ampicillin, cefotaxime, and acyclovir. The infant developed a severe coagulopathy secondary to liver dysfunction and DIC despite aggressive support with blood products including a continuous infusion of FFP. The initial laboratory evaluation and daily fluid intake and output are presented on Table I. A CT scan of the head was performed which revealed bilateral subdural hematomas and intracerebral hemorrhages (Fig. 1). An ophthalmologic evaluation showed bilateral retinal hemorrhages.

On the second hospital day, the infant developed renal insufficiency leading to fluid overload, generalized edema, ascites, and respiratory compromise. His trachea was incubated and mechanical ventilation was initiated. A continuous infusion of bumetanide was initiated but urine output was inadequate relative to the large volume of blood products administered to correct the coagulopathy. On the fifth hospital day, continuous venovenous hemofiltration was considered for fluid removal because of the need for escalating levels of respiratory support, which resulted from fluid overload. Despite a continuous infusion of FFP and frequent administration of platelets and cryoprecipitate, the coagulopathy was not correcting and a repeat CT scan of his brain revealed new bilateral intraventricular hemorrhages (Fig. 2). The infant was rapidly deteriorating, and the decision was made to start treatment with rFVIIa in a desperate attempt to control the newborn's bleeding, consumptive thrombocytopenia and increasing fluid overload.

The patient received two rFVIIa bolus infusions of 80 mcg/kg within the first 24 hr as well as continuous infusion at 16 mcg/kg/hr. Fluid intake was dramatically

decreased because of the reduced need for blood products (Fig. 3). The bumetanide infusion was discontinued and a continuous infusion of furosemide and chlorthiazide was initiated with good response. The patient's respiratory status improved in response to diuresis and his trachea was extubated on hospital day 20.

Continuous infusion rate of rFVIIa was titrated from 2.5 mcg/kg/hr to 40 mcg/kg/hr to maintain a normal PT. The patient's renal insufficiency and liver dysfunction gradually improved. Ultrasound examinations of both his liver and kidneys were normal. His AST, ALT, and total bilirubin peaked at 11,442 U/L, 2,104 U/L, and 25 mg/dl, respectively. His BUN and creatinine normalized although he did develop hypertension requiring treatment with enalapril.

On hospital day 37, the infant developed a fever (38.6°C) and blood cultures subsequently grew *Klebsiella pneumoniae*. A day later, he was noted to have swelling of his left lower extremity. His left femoral central venous line was removed and a Doppler study revealed an occlusive thrombus in the left common femoral vein, and nonocclusive thrombus in the left iliac vein. Doppler studies were done on the jugular veins, axillary veins, subclavian veins, and right femoral and iliac veins; there was no evidence of clot formation. The patient's platelet counts significantly decreased, and his fibrinogen level continued to be low. Factor VII level was at 34% prior to initiating anticoagulation treatment. Recombinant activated factor VII continued to be infused at 2.5 mcg/kg/hr throughout the anticoagulation period. The infant did not respond to low molecular weight heparin (LMWH), so unfractionated heparin (UH) was administered for 5 days. Table II describes the anticoagulation treatment, platelet counts and infused blood products during that period. Swelling of the left lower extremity resolved and the catheter-related blood stream infection was successfully treated with ceftazidime and gentamicin.

The infant's need for rFVIIa and blood product support diminished as his liver function improved and DIC resolved. Recombinant factor VIIa was administered

TABLE I. Laboratory Data Collected the First Five Hospital Days

Variables	Hospital days				
	Admission	2	3	4	5
Hemoglobin (13.2–20.0 g/dl)	21.6	15.5	11.8	7.9	11.8
Platelet count (140–450 × 10 ⁹ /L)	13	52	104	58	50
PT (8.6–12.0 sec)	26.9	23.6	29.9	18.2	19.7
PTT (18.5–29.0 sec)	66.8	50.2	64.9	41.2	40.8
Fibrinogen (200–400 mg/dl)	N/A	N/A	141	N/A	N/A
AST (15–49 U/L)	2,833	11,442	10,431	3,580	537
ALT (11–66 U/L)	453	1,952	2,104	1,501	167
Daily fluid input/output (ml)	277/122	514/209	743/320	632/363	806/395

Total daily fluid intake and output given during the same time are listed.

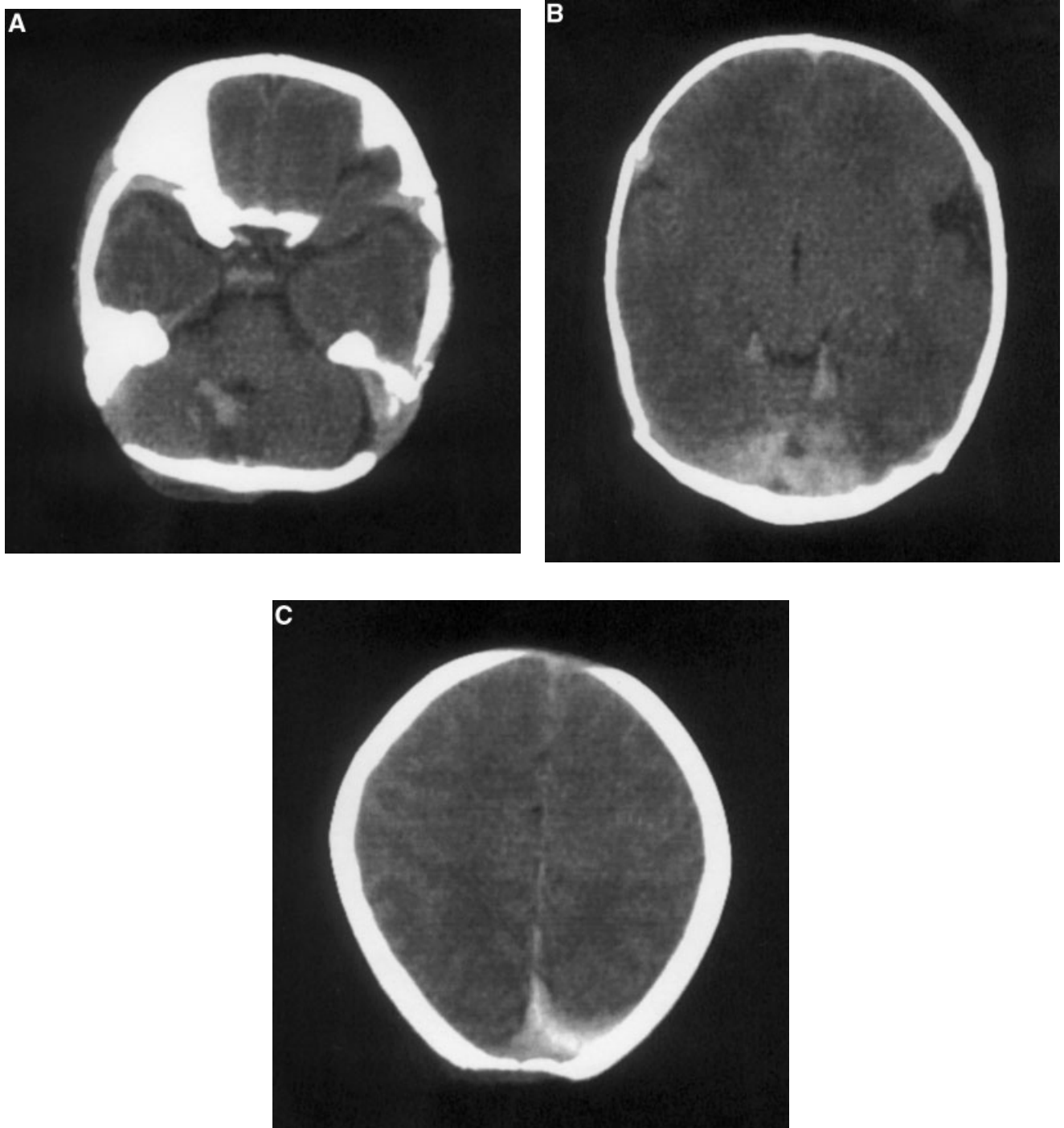


Fig. 1. (Hospital Day 1). Computerized tomograph (CT) of the head without contrast done on admission. Subdural hemorrhage along the tentorium and interhemispheric fissure (A). Small foci of parenchymal hemorrhage are present in the periventricular region adjacent to the posterior body right lateral ventricle (B). Hemorrhage along the medial right cerebellum (C).

until hospital day 50 when the platelet count reached $100 \times 10^3/\mu\text{l}$. The patient was discharged home after 62 days. Laboratory evaluation at the time of discharge revealed the following: BUN 6 mg/dl, creatinine 0.2 mg/dl, AST 216 U/L, ALT 88 U/L, bilirubin 4.3 mg/dl, PT 10.8 sec, hemoglobin 10.7 g/dl, and platelets count

$111 \times 10^3/\mu\text{l}$. A follow up CT of the brain showed a small residual subdural hematoma near the right cerebellar convexity (Fig. 4); intraparenchymal and intraventricular hemorrhages had resolved. At the time of discharge, the infant was alert, interactive, and fed vigorously. He exhibited symmetrical motor tone and strength. A month

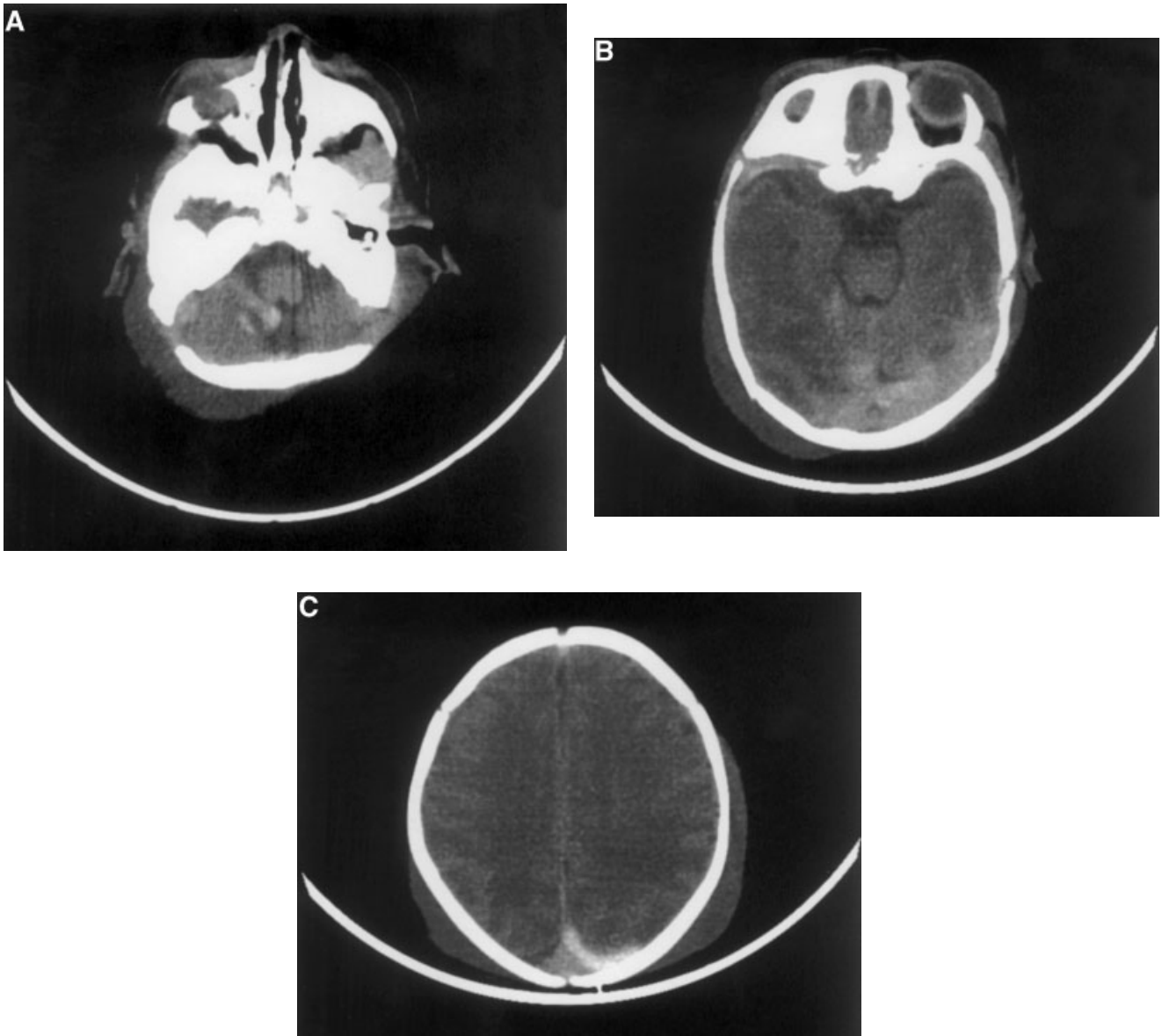


Fig. 2. (Hospital Day 4). CT of the brain without contrast. Increase in subdural hemorrhage with extension along the posterior interhemispheric fissure (A,B). Increased parenchymal edema (C).

later the baby was seen in clinic; he was gaining weight and reaching age appropriate milestones.

DISCUSSION

Disseminated echovirus infection in neonates causes severe hepatic injury with consequent DIC [1–6]. Liver biopsies done on neonates with echovirus infections revealed diffuse hemorrhagic necrosis of the endothelium lining hepatic arteries and veins with fibrin thrombi within these vessels [5,6]. As the synthetic function of the liver becomes compromised during the viral illness, many procoagulant (factors II, V, VII, IX, XIII, fibrinogen) and anticoagulant proteins (proteins C and S, antithrombin, AT) have significantly reduced plasma levels. Our patient

suffered severe liver damage, complicated by renal insufficiency and subsequent catheter related infection and thrombosis.

Factor VII is the major initiator of hemostasis. Factor VII has a short half-life (4 hr) and is hard to maintain at an adequate level with FFP, especially in the setting of severe hepatic dysfunction. In a healthy term neonate, the coagulation system is immature with low levels of procoagulant factors II, VII, IX and XIII, and anticoagulant proteins, protein C (PC), and AT. An infant with a sick liver has impaired synthesis of procoagulant and anticoagulant proteins, leading rapidly to hemorrhage.

Correction of coagulation factors in a failing liver is usually accomplished by the administration of FFP and cryoprecipitate. Large volumes of FFP are required to

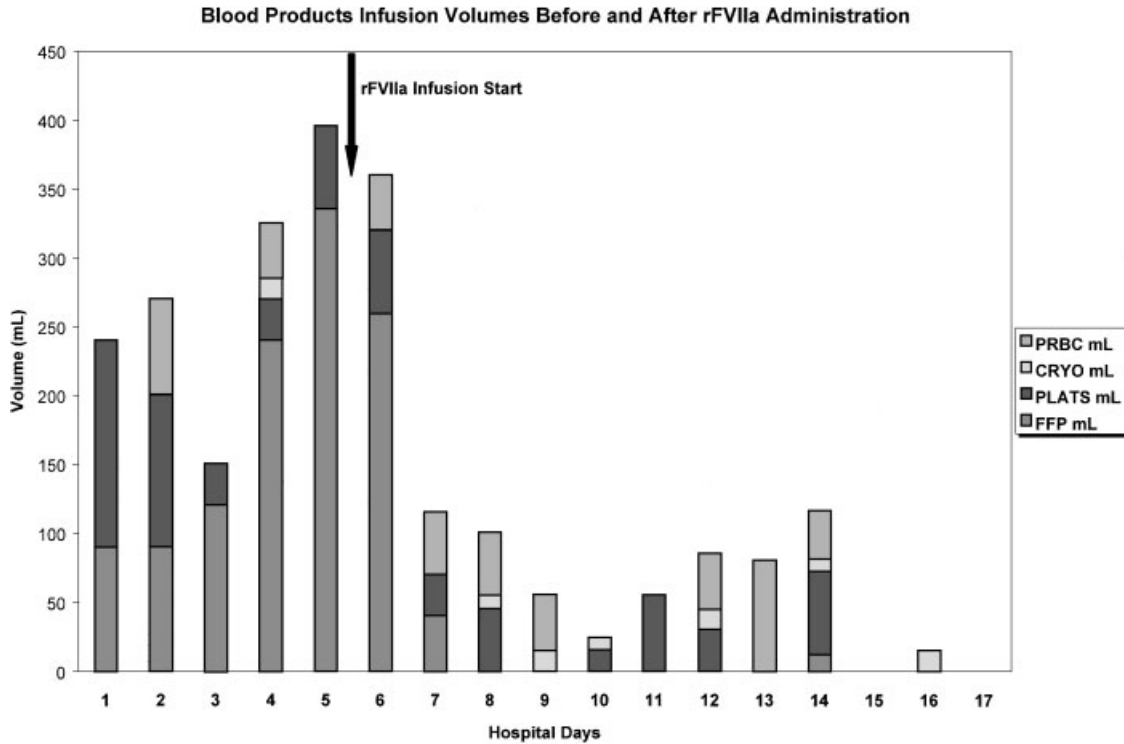


Fig. 3. Graphic representation of infused blood products (packed red cells, platelets, FFP, cryo) given before and after starting the rFVIIa infusion on hospital day 5.

supply the necessary levels of coagulation proteins essential for the maintenance of hemostasis. Infusions of FFP, cryoprecipitate, platelets, and packed red blood cells caused severe fluid overload in our patient, ultimately leading to acute respiratory failure. The infant’s bleeding diathesis was not correcting despite frequent administration of FFP and cryoprecipitate, which suggested inadequate levels of factor VII. The infant was critically ill with severe hepatic dysfunction and evidence of progressive CNS hemorrhage. Recognizing the potential risk of the procoagulant effect of rFVIIa in the setting of a systemic inflammatory state, we felt it was necessary to attempt to control the CNS bleeding. Administration of rFVIIa reduced the need for platelets, and packed red

blood cells. Decreasing the volume of fluid administered ultimately permitted correction of fluid overload and allowed liberation from mechanical ventilation. FFP and cryoprecipitate continued to be administered to increase the fibrinogen and AT levels as well as other coagulation factors. Platelets were given for platelet counts less than $50 \times 10^9/L$. Packed red blood cells were transfused to maintain adequate arterial oxygen content.

The patient’s response to heparin during treatment for his catheter related thrombosis may have been due to heparin binding simultaneously to thrombin and AT and accelerating the thrombin inactivation. LMWH binds to AT causing conformational changes in AT necessary to inactivate factor Xa, but not thrombin [7]. The

TABLE II. Anticoagulation Treatment for Left Femoral and Iliac Vein Thrombosis, and Laboratory Evaluation During rFVIIa Continuous Infusion

Variables	Hospital day									
	40	41	42	43	44	45	46	47	48	49
LMWH	X	X	X	X	X	D/c				
Anti Xa (0.40–1.10 U/ml)	N/A	<0.2	N/A	0.25	0.22					
Unfractionated Heparin						X	X	X	X	D/c
PTT (18.5–29.0 sec)	34.6	32.8	36.5	47.3	>250	155.6	57.3	71.1	60.4	54.4
Ddimer (0.00–0.45 µg/ml)	13.4	8.67	N/A	5.54	N/A	2.89	N/A	N/A	N/A	N/A
Fibrinogen (200–450 mg/dl)	145	157	139↑	231	270	N/A	190	N/A	144↑	N/A
Platelet count ($140\text{--}450 \times 10^9/L$)	29*	51*	79	37*	29*	27*	22*	34*	49*	104

X, medication given; D/c, medication discontinued; ↑, cryoprecipitate infusions; *, platelets infusions.

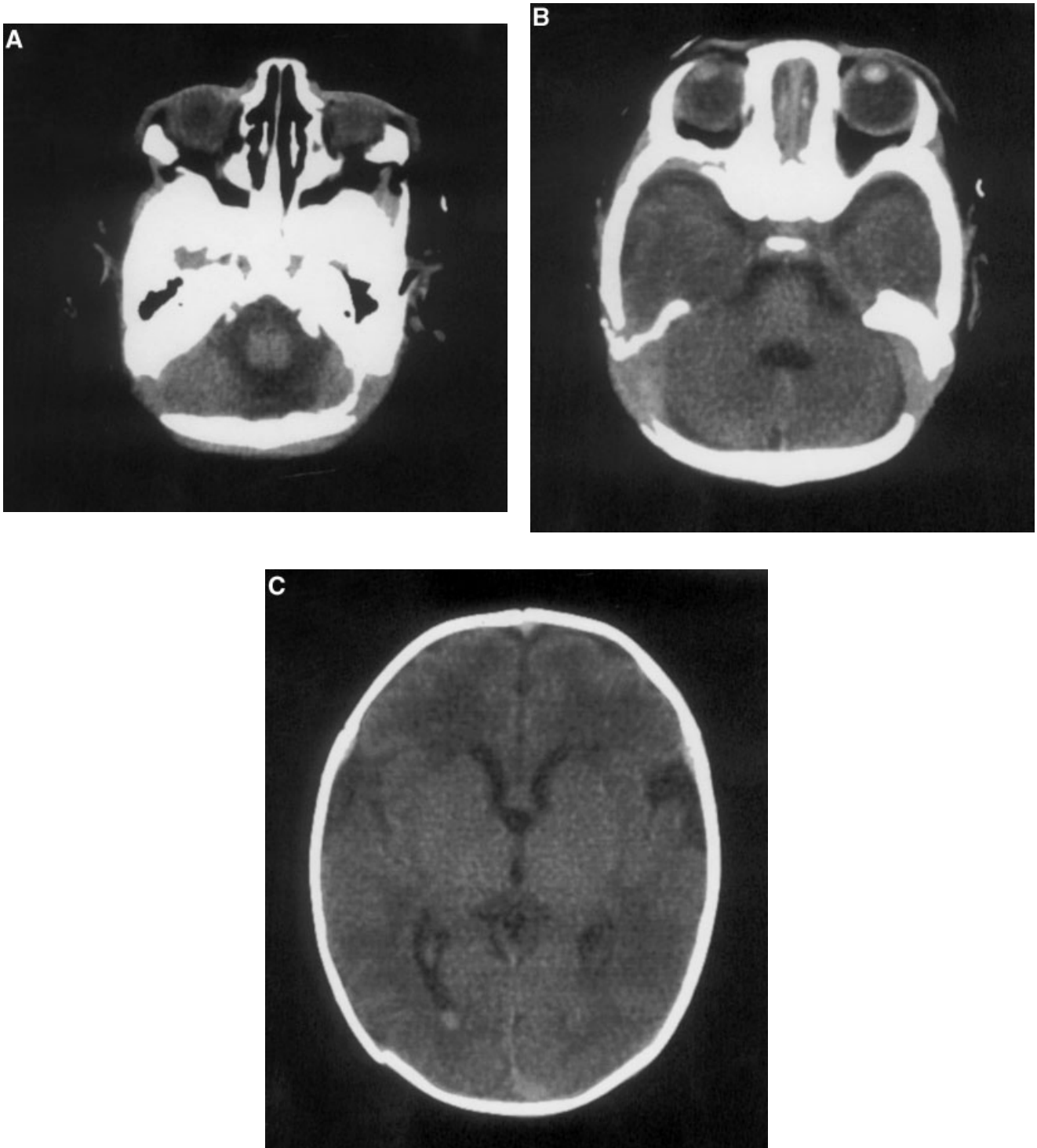


Fig. 4. (Hospital Day 22). CT of the brain without contrast. Near complete resolution of the left occipital subdural hematoma and tentorial hematomas (A,B). Decreased parenchymal edema (C).

patient's factor VII was 34% on hospital day 37, at the time of developing catheter related thrombosis, bacteremia, and significant drop in platelet counts. The continuous infusion of rFVIIa at 2.5 mcg/kg/hr was done to replace the factor VII deficiency secondary to liver dysfunction.

We followed the patient's clinical response to treatment, and the laboratory values readily available at our institution to modify our treatment. The patient's primary multiple organ dysfunction syndrome (MODS), systemic inflammatory response syndrome (SIRS), and bacteremia [19,20] resulted in vascular endothelial injury, coagulation

and fibrinolytic abnormalities, and thrombocytopenia. In retrospect, plasma samples could have been sent for the evaluation of thrombomodulin (TM), AT and PC. TM inactivates thrombin and activates PC thus prevents excessive blood coagulation. TM may have played an important role in controlling the excess thrombin formation and stimulating the fibrinolytic process [21].

Recombinant factor VIIa was developed and FDA approved for the treatment of patients with hemophilia A and B with inhibitors against FVIII and IX, respectively. Recombinant factor VII has been used for the management of thrombocytopenia in patients with life threatening hemorrhage [7] and in clinically stable cirrhotic patients with prolonged PTs [8–10]. Recent studies describe rFVIIa mechanism of hemostatic action. Recombinant factor VIIa may bind to tissue factor and subsequently activate factor X leading to thrombin generation. A tissue factor independent pathway has also been described showing rFVIIa binding to activate platelet surface and activating factor X. Thrombin generation follows, and a stable fibrin clot is formed, even in the absence of an ideal platelet plug [11–13]. Several case reports in recent publications described the use of rFVIIa in premature infants with severe hemorrhagic episodes [14,15], bleeding prevention prior to procedures in neonates with liver failure [16], DIC in children with dengue hemorrhagic fever and hepatoblastoma [17], and correction of coagulopathy following cardiac surgery [18]. Administration of rFVIIa appears to have stabilized the coagulation process and ultimately allowed for full liver recovery from the viral insult. Controlled randomized studies are needed to prove the safety and efficacy for the use of rFVIIa in other than FDA approved indications.

REFERENCES

1. Ho-Yen DO, Hardie R, McClure J, et al. Fatal outcome of echovirus 7 infection. *Scand J Infect Dis* 1989;21:459–461.
2. Ventura KC, Hawkins H, Smith MB, et al. Fatal neonatal echovirus 6 infections: Autopsy case report and review of the literature. *Mod Pathol* 2001;14(2):85–90.
3. Arnon R, Naor N, Davidson S, et al. Fatal outcome of neonatal echovirus 19 infection. *Pediatr Infect Dis J* 1991;10(10):788–789.
4. Chambon M, Delage C, Bailly JL, et al. Fatal hepatic necrosis in a neonate with echovirus 20 infection: Use of the polymerase chain reaction to detect enterovirus in liver tissue. *Clin Infect Dis* 1997;24:523–524.
5. Wang J, Atchison RW, Walpusk J, et al. Echovirus hepatic failure in Infancy: Report of four cases with speculation on the pathogenesis. *Pediatr Develop Pathol* 2001;4:454–460.
6. Mostoufizadeh MG, Lack EL, Gang DL, et al. Postmortem manifestation of echovirus sepsis in five newborn infants. *Hum Pathol* 1983;14(9):818–823.
7. Esmon CT. Blood Coagulation. In: Nathan DG, Orkin SH, Ginsburg D, Look TA, editors. *Nathan and Oski's Hematology of Infancy and Childhood*, 6th edition. Philadelphia, PA: WW Saunders Company, 2003. pp 1486–1487.
8. Gerotziakas GT, Zervas K, Arzoglou P, et al. On the mechanism of action of recombinant activated factor VII administered to patients with severe thrombocytopenia and life threatening haemorrhage: Focus on prothrombin activation. *Br J Hematol* 2002;117:705–708.
9. Bernstein DE, Jeffers L, Erhardsten E, et al. Recombinant factor VII corrects prothrombin time in cirrhotic patients: A preliminary study. *Gastroenterology* 1997;113:1930–1937.
10. Puetz JJ, Bouhasin JD. Use of recombinant factor VIIa to control bleeding in an adolescent male with severe hemophilia A, HIV, thrombocytopenia, hepatitis C, and end stage liver disease. *Am J Hops Palliate Care* 2002;19(4):277–282.
11. Hoffman M, Monroe DM, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: Thoughts on the mechanism of action of high dose activated factor VII. *Blood Coagul Fibrinolysis* 1998;1(Suppl):S61–S65.
12. Kjalke M, Ezban M, Monroe DM, et al. High dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia like conditions in a cell based model system. *Br J Haematol* 2001;114(1):114–120.
13. Hoffman M, Monroe DM. The action of high dose factor VIIa (FVIIa) in a cell based model of hemostasis. *Dis Mon* 2003;49(1):14–21.
14. Veldman A, Fischer D, Virgo B, et al. Life threatening hemorrhage in neonates: Management with recombinant activated factor VII. *Intensive Care Med* 2002;28:1635–1637.
15. Chuansumrit A, Nuntnarumit P, Okascharoen C, et al. The use of recombinant activated factor VII to control bleeding in a preterm infant undergoing exploratory laparotomy. *Pediatrics* 2002;107:169–171.
16. Young G, Nugent DJ. Prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa. *Hematology* 2001;6:341–346.
17. Chuansumrit A, Chantarojanasiri P, Isarangkura P, et al. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2000;11(Suppl):S101–S105.
18. Tobias JD, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Pediatr Crit Care Med* 2003; 4:49–51.
19. The ACCP/CCM Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
20. Hayden WR. Sepsis terminology in pediatrics. *J Pediatr* 1994; 124(4):657–658.
21. Ueno H, Hirasawa H, Oda S, et al. Coagulation/fibrinolysis abnormality and vascular endothelial damage in the pathogenesis of thrombocytopenic multiple organ failure. *Crit Care Med* 2002; 30(10):2242–2248.