Recombinant Factor VIIa and Activated Prothrombin-Complex Concentrate Administration in the Management of Bleeding, Coagulopathy and Intractable Coagulopathy in Pediatric Patients Undergoing Invasive Medical Procedures or Surgery

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ABSTRACT

Coagulation factor VII (FVII) is a vitamin K dependent glycoprotein of the extrinsic pathway and initiates coagulation by binding to tissue factor. Activated prothrombin-complex concentrate ([APCC] FEIBA), an activated prothrombin complex concentrate that is plasma-derived, has also been demonstrated to bypass the need for FVIII or factor IX, resulting in hemostasis. Both APCC and recombinant factor VII ([rFVIIa] NovoSeven) are used for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or IX and in those with congenital Factor VII deficiency. The aim of the present study was to evaluate the clinical outcomes of APCC or rFVIIa therapy in pediatric patients (that bleeding or coagulopathy) undergoing invasive medical procedures or surgery. Twenty four patients hospitalized in pediatric clinics for intractable bleeding disorders and coagulopathies. The drugs were administered in a total of 35 episodes (25 episodes for APCC and 10 episodes for rFVIIa). Total blood count, blood biochemistry, coagulation tests and appropriate radiological assessments were performed in each patient. Survival times were calculated for each patient. The mean values of prothrombin time (PT) was 29.4±16.5 second, partial thromboplastin time (PTT) was 70.2±43.8 second and fibrinogen level was 247.8±130.2 mg/dl. The mean values after the administration of APCC or rFVIIa were 16.6±7.2 seconds, 41.2±16.0 seconds and 290.3±146.9 mg/dl, PT, PTT and fibrinogen level, respectively. The improvements in the corresponding values after therapy were statistically significant. APCC and rFVIIa can be used to prevent coagulopathy and cessation bleedings. Thus, these concentrates may be effective in reducing the incidence of thrombocytopenia and coagulopathy.

Key Words: Bleeding, Coagulopathy; APCC, rFVIIa, Pediatric patients, Thrombocytopenia

ÖZET

Kanama, Koagulopati ya da Durdurulamayan Koagulopatili Pediatrik Hastalarda İnvazif ya da Cerrahi Girişimin Yönetiminde Rekombinan Faktör VII ve Aktive Protrombin Kompleks Kansantresi Verilmesi

Koagulasyon faktör VII (FVII), ekstrinsik yolda vitamin K bağımlı bir glikoprotein olup, doku faktörüne bağlanması ile koagulasyonu başlatır. APCC, plazmadan elde edilmiş aktive bir protrombin kompleks konsantresi olup, FVIII ya da FIX'a gereksinim duymadan hemostazis gerçekleştirebildiği gösterilmiştir. APCC ve rFVIIa, doğumsal FVII eksikliği ya da inhibitör geliştiren FVIII ya da FIX eksikliği olan hemofili hastalarının kanama ataklarının tedavisi için kullanılır. Bu çalışmadaki amaç; kanama ya da koagulopatili pediatrik hastalarda invazif ya da cerrahi girişim için kullanılan APCC ya da rFVIIa'ın klinik sonuçlarını değerlendirmektir. Hastaneye yatırılmış ve durdurulamayan kanama ve koagulopatisi olan 24 hasta çalışmaya alındı. 35 atakta ilaçlar verildi (25 atakta APCC ve 10 atakta rFVIIa). Tam kan sayımı, kan biyokimyası, koagulasyon testleri ve uygun radyolojik değerlendirmeler her bir hasta için yapıldı. Her bir hastanın yaşam süreleri hesaplandı. Ortalama PT 29.4±16.5 saniye, PTT 70.2±43.8 saniye ve fibrinojen seviyesi 247.8±130.2 mg/dl idi. APCC ya da RFVIIa verildikten sonra ise sırasıyla 16.6±7.2 saniye, 41.2±16.0 saniye ve 290,3±146,9 mg/dl olduğu görüldü. Tedavi sonrasındaki değerlerdeki düzelme istatistiksel olarak ta anlamlı idi. APCC ve rFVIIa kanamnın durdurulmasında ya da koagulopatinin önlenmesinde kullanılabilir. Böylece de, bu konsantreler trombositopeni ve koagulopati insidansının azaltılmasında etkili olabilirler.

Anahtar Kelimeler: Kanama, Koagulopati, APCC (FEIBA), rFVIIa, Pediatrik hastalar, Trombositopeni

INTRODUCTION

Blood coagulation and fibrinolysis are defence systems of the hemostasis. Fibrinolysis removes fibrin clots, and restores blood flow. Alpha thrombin generation and fibrin clot formation protect the vasculature from injury and blood loss. The platelets and cell membrane proteins carry out key roles in the coagulation and fibrinolysis processes. Hemostasis is actively maintained by the vascular system. There are two procoagulant pathways. These are extrinsic and intrinsic pathway. The denomination of these two procoagulant pathways is based on clinical evidence of bleeding in patients. Therefore, deficiencies of factors in the extrinsic pathway (factors II, V, VII, VIII, IX, X, protein C-S-Z and others) can cause severe bleeding diathesis, while deficiencies of factors involved in the intrinsic pathway (factor XII, XI, prekallikrein, kininogens and Fitzgerald factor) do not lead to severe bleeding, even after surgical operations. Coagulation factors exist in inactive or procoagulant forms in human plasma. Factors of the intrinsic pathway are responsible for the contact activation of blood coagulation.[1,2]

Coagulation factor VII (FVII) is a vitamin K dependent glycoprotein of the extrinsic pathway and initiates coagulation by binding to tissue factor (TF). Tissue factor is a component of the deep layer of the walls of the blood vessels and is only present in the blood after injury or trauma. Once FVII binds with TF, FVII is converted to its active form (FVIIa) and facilitates activation of factors X and IX leading to thrombin production. Thrombin production then leads to activation of platelets and formation of a clot. Recombinant factor VIIa (rFVIIa) is a recombinant clotting factor that bypasses the need for factor VIII or IX, allowing clotting to occur. APCC, an activated prothrombin complex concentrate that is plasma-derived, has also been demonstrated to bypass the need for FVIII or FIX, resulting in hemostasis. Both APCC and rFVIIa are used for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or IX and in those with congenital Factor VII deficiency. These activated coagulation factor concentrates are also approved for the prevention of bleeding prior to surgical interventions or invasive procedures in similar patients. Apart from these major indications, these agents are also used in a wide variety of off-label indications including surgery or trauma-related bleeding, reversal of anticoagulation therapy, other coagulation defects (e.g. von Willebrands disease, factor V deficiency and factor XI deficiency) and finally as a rescue intervention in patients with intractable bleeding despite other therapeutic measures.[1-14]

The aim of the present study was to evaluate the clinical outcomes of APCC or rFVIIa therapy in patients with intractable coagulopathy or hemorrhage, patients with coagulopathy which otherwise could not be operated or patients in whom invasive diagnostic or therapeutic procedures were indicated.

PATIENTS AND METHODS

Twenty four patients hospitalized in pediatric clinics for intractable bleeding disorders and coagulopathies from January 2003 through May 2005 were included in the study. There were 35 episodes of intractable bleeding and coagulopathy in these patients. Thirteen patients died (54.2%) while the remaing 11 (45.8%) patients survived. Of those 13 patients who died, 4 cases were lost due to repeating bleeding episodes and 9 patients due to sepsis or the underlying disease. Intractable bleeding and coagulopathy persisted despite the administration of blood and blood products. Some of the patients with intractable bleeding disorders required urgent surgical procedures for diagnostic or therapeutic purposes.

The drugs were administered in a total of 35 episodes (25 episodes for FEIBA (activated prothrombin-complex concentrate [APCC]) (50-100 IU/kg/dose) and 10 episodes for recombinant factor VIIa ([rFVIIa] NovoSeven) (60-120 μg/kg/dose)]; two patients received 4 infusions, 5 patients received 2 infusions on different times and 17 patients were infused only once. Thus each episode was considered on individual basis (1 episode= 1 patient) and the results were evaluated according to this assumption. Total blood count, blood biochemistry, coagulation tests and appropriate radiological assessments were performed in each patient. Survival times were calculated for each patient.

Statistical Analysis

Data was analyzed using the SPSS 10.01 (SPSS Inc., Chicago, IL) statistical package program. Paired-samples T test and log rank in the Kaplan-Meier tests were used for statistical analysis. The level of statistical significance was set at $p< 0.05$.

RESULTS

At enrollment, the mean age of the patients was 7.5±5.2 years (range, 2-16 years).Twenty patients were males (57.15%) and 15 patients were females (42.9%). The mean values obtained in the coagulation tests were as follows: prothrombin time (PT) 29.4±16.5 seconds, partial thromboplastin time (PTT) 70.2±43.8 seconds and fibrinogen level 247.8±130.2 mg/dl. The mean values after the administration of APCC or rFVIIa were 16.6±7.2 seconds, 41.2±16.0 seconds and 290.3±146.9 mg/dl, PT, PTT and fibrinogen level, respectively. The improvements in the corresponding values after therapy were statistically significant in both of PT ($p= 0.0001$) and PTT ($p= 0.0001$) but, fibrinogen was not statistically significant ($p= 0.073$, paired-samples T test).

The mean thrombocyte count was 135085.7 ±174678.4 /mm^3 and a thrombocyte count of 100000 and below was observed in 19 (54.3%) patients. Menorrhagia was present in 5 patients and these patients did not have coagulopathy. In 4 patients, the underlying cause for menorrhagia was thrombastenia and in one patient thrombocytopenia. Underlying diseases associated with coagulopathy or bleeding are presented in Table 1. Among these, malign diseases comprised 54.3% (19 cases) of all the cases. The total percentage of patients in whom coagulopathy was treated or bleeding was stopped with the administration of APCC or rFVIIa or who underwent surgery or invasive procedures was 77.1%. The severity of the bleeding decreased in 7 patients and in 1 patient bleeding continued. In this patient, disseminated intravascular coagulopathy (DIC) developed and in addition neutropenic sepsis and multiorgan failure were observed. Patients's overall survivals are depicted in Figures 1 and 2.

In total, 13 patients died, of whom 4 were lost due to repeating episodes of bleeding and 9 patients due to the adverse events associated with the underlying disease. Mortality rate was different significantly between the groups of patients with and without cancer (log rank $p= 0.0009$).

DISCUSSION

Vitamin-K dependent factors / proteins exhibit procoagulant (factor II, VII, IX and X) and anticoagulant (protein C, S and Z) activities. These proteins (except protein S and Z) are serine proteinases, and are related to the trypsin/chymotrypsin superfamily of proteins. Deficiencies of factors II, VII, IX and X are associated with increased bleeding while protein C and S deficiencies are associated with thrombotic tendencies. The synthesis of these proteins occur generally in the liver. Liver function in the biosynthesis of the clotting factors, dietary intake-ad-

Table 1. Underlying diseases in the patients enrolled in the study

	n	%	
I. Malignant diseases	**Total**	**19**	**54.3**
Solid tumors		**5**	**14.3**
Hepatoblastoma			
Newly diagnosed		2	
Relapsed / refractory		1	
Osteosarcoma		1	
Rhabdomyosarcoma		1	
Leukemia	**Total**	**14**	**37.1**
Acute myeloid lekemia (AML)			
Newly diagnosed		3	
Relapsed / refractory AML		6	
Acute lymphoblastic leukemia (T cell-ALL)		4	
Juvenile chronic myelo-monocytic leukemia (relapsed / refractory)		1	
II. Non-Malignant Diseases	Total	16	45.7
Congenital heart diseases		3	8.6
Newborn, premature, apnea		1	2.9
Thrombastenia or Thrombocytopenia	**Total**	**6**	**17.1**
Thrombastenia		4	
Thrombocytopenia		1	
Bernard-Soulier Syndrome and volvulus		1	
Liver insufficiency	**Total**	**6**	**17.1**
Wilson's cirrhosis		1	
Lupoid Hepatitis		1	
Milier tuberculosis (Tbc), Tbc meningitis and toxic hepatitis		1	
Hepatitis with unknown etiology		3	
Total		35	100.0

sorption of vit- K, and drug interactions can affect patients on anticoagulant therapy.[14,15] These activated forms of the vitamin K-dependent proteins play a key role in the coagulation process.[1,2]

In patients with hemophilia inhibitory antibodies to factor VIII and factor IX develop as a complication of factor replacement therapy. Factors that are replaced are rapidly inactivated by these inhibitors. Thus, intractable bleeding episodes occur in these patients. APCC (factor VIII inhibitor bypassing activity), an activated prothrombin complex concentrate and rFVIIa are used as hemostatic bypassing agents in treating patients with inhibitors. Prothrombin complexes have been used since 1980's[3] and activated prothrombin complex concentrates such as APCC have been reported to be more effective in patients with hemophilia compared to non-activated prothrombin complexes.[8,9] On the other hand, these complexes are also approved for the prevention of bleeding prior to surgical interventions or invasive procedures in hemophilia patients with inhibitory antibodies and their use is reported to prevent massive bleeding in these patients.[6-9] Allergic reactions, transient hypertension, dissemina-

Table 2. Indications and response to therapy with APCC or RFVIIa

Disorders	n (%)	Agent used	Response to agent	Invasive interventions
Thrombocytopenia, coagulopathy and bleeding	16 (45.6)			
Intracranial hemorrhage	4	F (n=4)	Reversal of thrombocytopenia and coagulopathy. Bleeding reduced	All patients were operated
Upper GIT bleeding	11	F (n=9)	Bleeding cessation (n = 8). Bleeding reduced (n = 1).	One patient with intestinal perforation was operated
		N (n = 2)	Bleeding cessation (n = 1). Bleeding reduced (n = 1).	
Lower GIT bleeding	1	N (n = 1)	Bleeding cessation.	
Coagulopathy and bleeding	4 (11.4)			
Lower GIT bleeding	2	N (n = 1)	Bleeding cessation.	
		N (n = 1)	Bleeding reduced.	
Upper GIT bleeding	1	F (n = 1)	Bleeding cessation.	
Renal hematoma secondary to warfarin used	1	F (n = 1)	Bleeding cessation, coagulopathy normalized	Patient was operated and a cannula was placed
Thrombocytopenia and Trombasthenia	6 (17.4)			
Menorrhagia	5	F (n = 2)	Bleeding cessation.	
		N (n = 3)	Bleeding cessation (n = 2) Bleeding continued (n = 1)	
Bernard-Soulier syndrome and volvulus (lower GIT bleeding)	1	F (n = 1)	Bleeding cessation	
Coagulopathy	9 (25.6)			
Liver biopsy	2	F (n = 1)	Coagulopathy normalized.	Biopsy was performed
		N (n = 1)	Coagulopathy normalized.	Biopsy was performed
Splenoportography		F (n = 1)	Coagulopathy normalized.	Splenoportography was performed
Massive pericardial effusion		F (n = 1)	Coagulopathy normalized.	Pericardial tube was placed.
Congenital heart disease Fallot tetrology, cyanotic spell and thrombocytopenia	1	N (n = 1)	Coagulopathy normalized.	Open heart surgery was performed
Intracardiac tumor metastasis	1	F (n = 1)	Coagulopathy normalized.	Open heart surgery was performed
Coagulopathy only	3	F (n = 2)	Coagulopathy normalized.	
		N (n = 1)	Coagulopathy normalized.	
Total Success	28 (77.1)			

GIT: Gastrointestinal tract, F: APCC, N: RFVIIa

ted intravascular coagulopathy (DIC) and thrombosis have been reported to be associated with the use of activated prothrombin complexes. But these complications will be minimal if these concentrates are used in recommended doses.[9] In our study, DIC was observed in only one patient. Activated factors in APCC activate other inactive factors in the coagulation coagulation. Thus factor IXa activates factor X and activated factor X (factor Xa) in turn activates factor II. Factor IIa activates protein C, enables fibrin monomer formation and additionally inhibits fibrinolysis by activating thrombin-activatable fibrinolysis inhibitor protein. It also enables the formation of factor XIIIa and thus stabilizes fib-

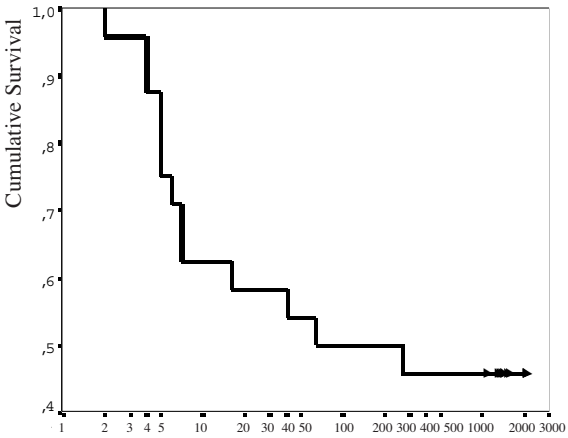

Figure 1. Overall survival

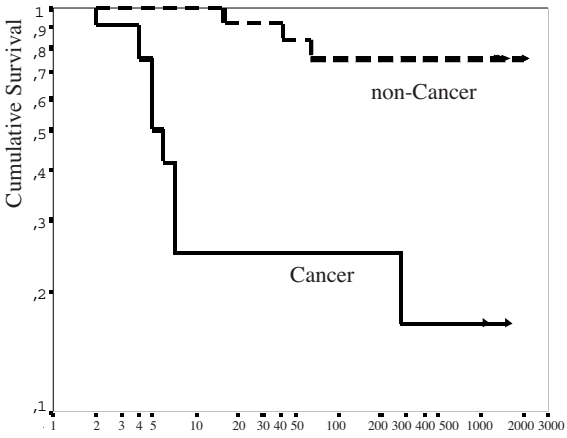

Figure 2. Overall survival in cancer and non-cancer

rin (intrinsic tenase activity). On the other hand, factor VIIa enables factor IXa and factor Xa synthesis.[1,2]

Successful use of recombinant FVIIa in a patient with severe haemophilia A during synovectomy was first reported by Hedner et al. in 1988.[10] This first report was followed by others reporting successful use of recombinant FVIIa in patients with factor deficiencies and inhibitory antibodies and recent clinical studies still indicate its effectiveness in similar clinical settings.[11,12,17-21] FVIIa initiates the extrinsic coagulation pathway and activates factors IX and X. It also autoactivates inactive FVII. Thus it can potentially reduce coagulopathy and help control bleeding.[1,2] In patients with coagulopathies, both APCC and rFVIIa can control coagulopathy and cessatton bleedings, thus enabling surgery and various invasive procedures in these cases. In a study conducted by Kluger et al.[22], 143 patients with severe blunt trauma were enrolled in a prospective, randomized, placebo-controlled study, in order to evaluate the safety and efficacy of intravenous rFVIIa. In this clinical trial, 30 polytrauma patients (placebo, n= 13; rFVIIa, n= 17) were identified as having traumatic brain injury and the incidences of ventilator-free days, intensive care unit-free days, and thromboembolic, serious, and adverse events within the 30-day study period were assessed in this cohort. The authors concluded that there were no statistically significant changes in the risk of mortality or thromboembolic or adverse events between the patients receiving rFVIIa or placebo. In another study published by Rizoli et al.[23] blunt and penetrating trauma patients were randomly assigned to rFVIIa or to placebo. The rFVIIa-treated coagulopathic subgroup needed significantly less red blood cell transfusion and the authors concluded that coagulopathic trauma patients derived particular benefit from the early administration of adjunctive rFVIIa therapy. Similarly, Stein et al.[24] reported a good clinical response to low dose rFVIIa in all their coagulopathic trauma patients in whom the need of packed red blood cells and fresh frozen plasma were significantly reduced after a low dose of rFVIIa. They observed thromboembolic events in 12 of the 81 patients (15%) enrolled in the study and only four of these events were thought to be related to the FVIIa administration. They concluded that low dose FVIIa rapidly and effectively treats mild to moderate coagulopathy following injury. On the other hand, Boffard and colleagues[25] report a decrease in the need of red blood cell transfusion with the use of rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma, compared to placebo, with a statistically significant reduction only in patients with severe blunt trauma. Other investigators[26] commented on the efficacy of activated recombinant factor VIIa in controlling critical bleeding during cardiothoracic surgery, reporting a statistically significant improvement in coagulation parameters and achievement of hemostasis in 8 out of 11 patients. In this small group of patients, transfusion of packed red cell and plasma decreased significantly after administration of rFVIIa.

The use of recombinant activated factor VII (rFVIIa) in the prevention of critical bleeding throughout the intraoperative phase of orthotopic liver transplantation significantly reduced blood loss and the need for platelets.[27] However, there are also reports which do not recommend the generalized use of rFVIIa to prevent or to control bleeding in nonhemophiliac patients.[28]

In the present study, APCC or rFVIIa administration prevented coagulopathy, cessation bleedings or enabled surgical or invasive procedures in totally 77.1% of all the patients enrolled. Bleeding was reduced in 7 patients and in only one patient bleeding continued. Menorrhagia was present in 5 patients and these patients did not have coagulopathy. In 4 patients, the underlying cause for menorrhagia was thrombastenia and in one patient thrombocytopenia. Underlying diseases associated with coagulopathy or bleeding in the patients are presented in Table 1.

We think that both agents can be successfully used in coagulopathic patients undergoing surgical or invasive procedures, to reduce the high tendency for bleeding. Although packed red blood cells, platelets and plasma should be used in patients with significant bleeding or coagulopathy, sometimes hemostasis can not be under control. We thought that one of the reason of hemostatic abnormalities is could be not to be avaliable sufficent plasma factor in plasma. Consequently coagulation pathway can not be activated. Active plasma factors, such as APCC and rFVIIa, provide the activation of coagulation pathway. Therefore life threatening hemorrhage can be prevented and invasive surgical procedures can be carried out like in our cases.

In conclusion, we think that in patients with coagulopathy and bleeding can not be managed with blood or blood product transfusions and thus are not considered eligible for life-saving surgical or invasive procedures, both APCC and rFVIIa can be used to prevent coagulopathy and cessatton bleedings. In cancer patients, neutropenia, infections and hepatotoxic effects increase the risk for bleedings secondary to bone marrow suppression and affect both morbidity and mortality. Additionally, we propose that in cases with various types of cancers, early or prophylactic administration of these active concentrates may be effective in reducing the incidence of serious thrombocytopenia and coagulopathy.

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