Looking toward the future: Treatment of bleeding episodes in the pediatric population with recombinant factor VIIa

rFVIIa in pediatric patients

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Introduction

In the perioperative period, coagulation disturbances in infants and children may result from congenital coagulation factor deficiencies; hepatic insufficiency or failure; disseminated intravascular coagulation (DIC) from sepsis, shock or closed head injury; dilution of coagulation factors following cardiopulmonary bypass (CPB) or large volume transfusions; and medications. Primary treatment includes reversal or elimination of the inciting event and when there is clinically significant or life-threatening bleeding, correction of coagulation function as guided by the coagulation profile including the prothrombin time (PT), International Normalized Ration (INR), partial thromboplastin time (PTT), fibrinogen level, and platelet count with the administration of cryoprecipitate, fresh frozen plasma (FFP), and/or platelet concentrates.

Despite its efficacy, problems exist with the administration of FFP including the transmission of infectious diseases, volume overload, anaphylactoid reactions, and alterations in serum ionized calcium which may lead to hypotension, cardiovascular compromise, and even cardiac arrest.[1] The time required for obtaining the blood type followed by thawing and administration of FFP may be significant leading to a prolonged period of time with an uncorrected coagulopathy. Additionally, in selected cases, despite the administration of significant volumes of FFP, coagulation disturbances may persist.

Factor VII plays a key role in both the extrinsic and the intrinsic coagulation cascade. Factor VII is activated after contact with tissue factor that is exposed at the site of tissue injury. Activated factor VII can then directly activate factor IX of the intrinsic cascade. Activated factor IX with activated factor XIII can then activate factor X. Alternatively through the extrinsic cascade, activated factor VII can directly activate factor X. Activated factor X can then enter the common cascade leading to the conversion of prothrombin to thrombin and subsequent fibrin formation.

Recombinant DNA technology provides the means for the production of pharmacologic quantities of various coagulation factors including factor VII. In 1988, a patient with hemophilia and inhibitors against factor VIII, who was undergoing knee surgery, was the first patient to be treated with recombinant factor VIIa (rFVIIa). The majority of experience in both the adult and pediatric population with rFVIIa is in the treatment of patients with hemophilia who have developed auto-antibodies against factor VIII (inhibitors) thereby making subsequent infusions of factor VIII ineffective. In this scenario, rFVIIa has been shown to effectively control bleeding. Following the demonstration of its efficacy in the hemophilia population, there has been an increasing body of clinical experience with rFVIIa in the non-hemophiliac population with coagulation disturbances of various etiologies. Although the majority of this experience is in the form of isolated case reports or case series, the literature has been uniformly positive. Experience with rFVIIa in life-threatening and difficult to control coagulation dysfunction has also extended into the pediatric-aged population. The following manuscript reviews the clinical experience with rFVIIa in the pediatric population, discusses potential dosing regimens, and provides preliminary guidelines regarding its potential applications in the age group.

Experience in the pediatric population

Hepatic insufficiency:

Outside of the hemophilia population, the largest clinical experience with rFVIIa in pediatric-aged patients is in the setting of altered coagulation function related to hepatic insufficiency and/or hepatic failure of various etiologies. Chuansumrit et al. reported the successful use of rFVIIa in 3 children with hepatic failure and coagulation disturbances related to either dengue fever or following hepatic resection.[2] All three patients had active clinical bleeding. In the first two cases, rFVIIa was used when clinical bleeding continued despite the administration of FFP and cryoprecipitate while in the third case, only rFVIIa was administered. The dosing regimen, which the authors noted was adopted from the experience with rFVIIa in patients with hemophilia, included an initial bolus dose of 90 mcg/kg followed by a continuous infusion of 16.5 mcg/kg/hr. The infusion was continued for 18, 40, and 72 hours in the three patients with control of clinical bleeding and correction of the coagulation profile. A second case series reported by Chuansumrit et al included 5 children with coagulopathy and liver failure related to hepatitis, histiocytosis, biliary atresia, autoimmune processes, and hepatoblastoma.[3] There was an ongoing coagulation disturbance in all of the patients despite the administration of FFP (40 mL/kg). All of the patients required an invasive procedure including upper endoscopy for hematemesis in 3 and liver biopsy in 2. Recombinant FVIIa (40 mcg/kg) resulted in normalization of the PT and the procedures were performed without problems. One patient received 40 mcg/kg of rFVIIa every 6 hours for 48 hours due to the recurrence of GI bleeding. Additional information regarding the efficacy or rFVIIa in infants and children with hepatic dysfunction and coagulation disturbances is available from 6 additional patients who received rFVIIa (table 1).[4-6]

Perioperative administration:

Recombinant VIIa has also been administered in the perioperative setting in the pediatric age group. Four of these reports describe the use of rFVIIa following cardiac surgery.[7-10] Al Douri M et al. reported the successful use of rFVIIa in a case series of 5 patients with bleeding and coagulation dysfunction following cardiac surgeon.[7] One of the patients was a 2.5 year old child with an intraoperative blood loss of 4.5 liters during repair of an atrial septal defect and an arterial switch procedure for transposition of the great vessels. The bleeding, which continued despite the administration of FFP and platelets, ceased after a single dose of rFVIIa (30 mcg/kg). Tobias et al. reported similar efficacy in the control of bleeding following cardiac surgery and cardiopulmonary bypass in a 4 month old, 3.7 kg infant.[8] Chest tube output averaged approximately 10 mL/kg/hr for the first 3 postoperative hours and laboratory evaluation revealed a PT of 36.6 seconds (normal PT, 11.5-13.2 seconds), INR 6.8 (normal INR, 0.8-1.4), PTT 96.5 seconds (normal, 22.9-31.7 seconds) with a platelet count of 80,000/mm^3. Following rFVIIa, the chest tube out was 3 mL/kg/hr for the subsequent 3 hours and there were no additional bleeding concerns. Leibovitch et al. reported the successful cessation of pulmonary hemorrhage following the administration of rFVIIa.[9] The patient was a 10 month infant with trisomy 21 who was status post repair of an AV canal. On the second postoperative day, there was the acute onset of bleeding from the ET tube. Bronchoscopy demonstrated diffuse bleeding within the tracheobronchial tree. The bleeding persisted despite the administration of FFP, platelets and tranexamic acid. A total of 4 doses of rFVIIa (100 mcg/kg) were administered over an 8-9 hour period. The authors reported cessation of bleeding and no further need for blood products.

Tobias et al. have also reported experience with the use of rFVIIa to decrease chest tube bleeding following cardiac surgery in children.[10] Recombinant FVIIa was administered to 9 children (mean age: 9 $\pm$ 4 years) following repair of tetralogy of Fallot (6), closure of ventricular septal defect (1), closure of sinus venosus atrial septal defect (1), and mitral valve repair (1) who had chest tube output greater than 3 mL/kg/hr for the first 3 postoperative hours. Chest tube output for the initial 3 hours, prior to the administration of rFVIIa, was 5.8 $\pm$ 2.8 mL/kg/hr and decreased to 2.0 $\pm$ 1.3 mL/kg/hr for the 3 hours following the administration of rFVIIa (p=0.002). In a cohort of control patients that did not receive rFVIIa, chest tube output for the first 3 postoperative hours was 1.6 $\pm$ 0.9 mL/kg/hr and 1.2 $\pm$ 0.6 mL/kg/hr for the next 3 hours (p=NS when compared to chest tube output for the 3 hours following rFVIIa in patients who received rFVIIa). No adverse effects related to the use of rFVIIa were noted.

Additional perioperative experience with rFVIIa includes case reports regarding its efficacy in various scenarios including: 1) coagulopathy and bleeding following thoracic surgery related to an intraoperative cardiac arrest and the development of DIC[11], 2) dilutional coagulopathy and bleeding following large volume blood transfusions during posterior spinal fusion in two children[12], 3) bleeding following abdominal surgery and large volume transfusions in an 1120 gram, 29 week preterm infant[13], 4) prior to placement of intracranial pressure monitoring/ventriculostomies in 3 other patients[14], and 5) prior to removal of an intra-aortic balloon pump in a 19 year who suffered a cardiorespiratory arrest with ongoing cardiovascular dysfunction during renal transplantation[15] (table 2).

Administration to patients with platelet dysfunction:

Given its mechanism of action (see article by Dr. Guy Young regarding the current theory regarding the mechanisms of coagulation and the interaction of platelets and coagulation factors), rFVIIa may also promote hemostasis in both quantitative and qualitative platelet disorders. Eight to ten pediatric patients with qualitative platelet disorders have been successfully treated with rFVIIa[16-20]. The etiologies of the platelet dysfunction have included both inherited (Glanzmann's thrombasthenia, Bernard-Soulier syndrome, and von Willebrand's disease type III) and acquired defects (uremia). In the majority of cases, the problem has been spontaneous mucosal hemorrhage (epistaxis or oropharyngeal) with one report of prophylactic administration prior to a surgical procedure[16]. In addition to its effects in qualitative platelet disorders, rFVIIa has also been shown to be effective in the presence of thrombocytopenia in an animal model.[21]

Initial clinical experience at the University of Missouri

We have published our initial clinical experience over a 6-month period with rFVIIa administration.[22] During the 6-month review period, twenty-two doses of rFVIIa were administered to 10 patients ranging in age from 3 months to 19 years and in weight from 3.7 to 49 kgs. The clinical indication for rFVIIa included active bleeding (17 doses) or prophylactic correction of coagulation function prior to a procedure (5 doses). The 5 procedures included placement of an invasive device in 3 patients (intracranial pressure monitor in 2 patients and pericardial drainage catheter in 1 patient) or removal of an invasive device in 2 patients (intra-aortic balloon pump and transthoracic pulmonary artery catheter).

In all 10 patients, prior to the administration of rFVIIa, the PT was greater than 15 seconds, the INR greater than 1.5, and the PTT greater than 35 seconds (normal values at our institution are: PT $\leq$ 13.5 seconds, INR 0.8 to 1.2, and PTT $\leq$ 35 seconds). The etiology of the coagulation disturbances included dilutional in 4 patients (large volume transfusion in 3 and following cardiopulmonary bypass in 1), DIC in 4 patients (head trauma in 2, status post cardiac arrest in 1, and septic shock in 1), and hepatic insufficiency in 2 (cystic fibrosis in 1 and cholestasis from prolonged parenteral nutrition in 1). Seven of the 10 patients had received FFP (20-40 mL/kg) prior to the administration of rFVIIa and 4 of 10 had received cryoprecipitate to achieve a fibrinogen level greater than 100 mg/dL. Despite this therapy, the prolongation of the INR, PT and PTT persisted. In all 10 patients, the platelet count was greater than 100,000/mm^3 and the fibrinogen level was $\geq$ 100 mg/dL at the time of administration of rFVIIa (dose ranging from 50 to 100 mcg/kg). Following the 22 doses of rFVIIa, the PT was $\leq$ 13.5 seconds in 19 cases, the INR was $\leq$ 1.2 in 20 cases and the PTT was $\leq$ 35 seconds in 9 cases. In the 2 cases in which the INR did not correct to $\leq$ 1.2, the INR was 1.4 and 1.8. These two patients received doses of rFVIIa on the lower end of the dosing range of 50 to 100 mcg/kg (65 and 72 mcg/kg). Seventeen doses of rFVIIa were administered in the Pediatric ICU while 5 doses were administered intraoperatively. Five patients received a single dose and 5 patients received multiple doses. In all cases, the clinically significant bleeding ceased or the invasive procedure was performed without incident. No adverse effects related to rFVIIa were identified.

Summary

In any bleeding scenario, attempts should be made to exclude surgical causes; the etiologic factors contributing to the coagulopathy (hypoperfusion, acidosis, hypothermia, inadequate reversal of heparin) should be reversed, and correction of the defective coagulation function instituted.

Correction of coagulation function should focus on platelet count and function as well as clotting factors including fibrinogen concentration. Given our experience and that reported in the literature, several scenarios in pediatric-aged patients may be present in which rFVIIa should be considered. Recombinant FVIIa may be indicated in coagulopathic states to control active bleeding or to correct coagulation function prior to an invasive procedure (placement of or removal of an invasive device). Recombinant FVIIa may be considered when the coagulopathy does not respond to FFP, time is not available to wait for blood typing, thawing, and administration of FFP, there are concerns regarding the potential hemodynamic effects of FFP, or religious objections to the use of blood products. When compared with rFVIIa, potential problems with FFP include adverse hemodynamic effects[1], anaphylactoid reactions, volume overload, infectious disease transmission, and the previously mentioned, time constraints related to blood typing, etc. Recombinant FVIIa can be quickly reconstituted from powder with a small volume of sterile water and administered intravenously over 2-3 minutes.

Our experience with this agent and the reports from the literature lend further evidence for the efficacy of rFVIIa even when the coagulation defect fails to correct following the administration of FFP. There are now reports regarding the administration of rFVIIa to approximately 50-60 non-hemophiliac pediatric patients with acquired coagulation disturbances. Applications have included patients with coagulation dysfunction of various etiologies as well as inherited disorders of platelet function. Although the clinical experience is somewhat limited, no significant adverse effects have been noted in the pediatric-aged patient. As rFVIIa requires tissue factor for activation and tissue factor is released only with vascular damage, the risk of excessive thrombogenesis should be limited. However, especially in the pediatric cardiac surgical patient, there are no data regarding its use in patients with vascular anastomoses such as systemic-to-pulmonary shunts, which may be at high risk for thrombotic complications. Prospective, randomized trials are needed to clearly define the efficacy and adverse effect profile of this agent. Since rFVIIa does not correct other factor deficiencies, the coagulopathy may recur once the rFVIIa is cleared suggesting that other therapies may be needed to correct coagulation function.

Dosing recommendations in the pediatric-aged patient are extrapolated, in part, from the adult literature supplemented by information from the pediatric hemophiliac population. Bolus doses have ranged from 40 to 100 mcg/kg in the non-hemophiliac population, pediatric population including our clinical experience. With ongoing bleeding or risk for bleeding, repeated doses at 2-6 hour intervals have been administered. In addition to bolus dosing, there are reports of the use of a continuous infusion (20 to 30 mcg/kg/hr) following the bolus to maintain hemostatic levels of rFVIIa. When compared to adults, the pharmacokinetics in pediatric-aged patients demonstrate a shorter half-life and increased clearance.[23]

Given its potential therapeutic impact, rFVIIa warrants further investigation in the pediatric population. In addition to its effects on coagulation function, preliminary data report augmentation of platelet function suggesting a potential role in patients with bleeding and qualitative platelet disorders. Despite its potential benefits, cost remains a consideration. rFVIIa is approximately $0.85 per microgram. Such information must be factored in when considering the cost of the agent itself versus cost of blood products, repeated coagulation testing as well as potential benefits of decreased administration of homologous blood products, decreased ICU stays and potentially decreased patient morbidity and mortality.

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Table 1: Reports of rFVIIa use in infants and children with hepatic dysfunction

Author & reference	*Number of patients (age)*	*Clinical scenario*	*Outcome*
Kalicinski P et al[4]	2 (2.5 yr, 6 yr)	Hepatic transplantation	Perioperative coagulopathy despite FFP and cryoprecipitate with INR or 5.7 and 6.9. Patient #1 received 100 mcg/kg prior to incision and 2 hours later resulting in an INR of 0.7 to 1.1 during the surgery. Patient #2 received one dose preoperatively and the INR was 1.1 to 2.4 intraoperatively.
Young G, Nugent DJ[5]	3 (neonates)	Prior to invasive procedures	Three neonates requiring open liver biopsy and/or central line placement. Coagulopathy previously unresponsive to FFP. In 2 patients, rFVIIa was administered in a dose of 100 mcg/kg every 2 hours during the procedure and then every 6 hours following the procedure. In the third patient, a bolus of 100 mcg/kg was followed by an infusion of 30 mcg/kg/hr for 24 hours postoperatively. rFVIIa corrected the PT and the procedures were completed without incident.
Tobias JD, Berkenbosch JW[6]	1 (11 mos)	Upper GI bleeding	Patient with cholestasis, hepatic insufficiency (related to prolonged parenteral nutrition) and coagulopathy previously unresponsive to FFP. Developed life-threatening upper GI bleeding from esophageal varices requiring 40 mL/kg of packed RBC's. Bleeding ceased after the administration of rFVIIa (90 mcg/kg).

Table 2: Reports of rFVIIa use in infants and children during the perioperative period

Author & reference	*Number of patients (age)*	*Clinical scenario*	*Outcome*
Kenet G[10]	1 (6 yr)	thoracic surgery	Intraoperative arrest and coagulopathy. rFVIIa (90 mcg/kg) leads to correction of coagulation function and cessation of clinical bleeding.
Tobias JD et al[11]	2 (8 yr, 13 yr)	Posterior spinal fusion	Intraoperative blood loss and coagulopathy. No response following 20-30 mL/kg of FFP. rFVIIa (90 mcg/kg) leads to correction of coagulation function. PT decreased from 16.8 to 10.6 and 16.9 to 12.6 while INR decreased from 1.7 to 0.8 and 1.5 to 0.9 in the two patients respectively.
Chuansumrit A et al[12]	1 (1120 gram infant)	Intra-abdominal surgery	Ongoing intra-abdominal bleeding unresponsive to administration of large blood product transfusions including 103 mL/kg FFP, 7 mL/kg cryoprecipitate, and 67 mL/kg platelets. Recombinant FVIIa (40 mcg/kg) resulted in cessation of bleeding from umbilicus, surgical site and endotracheal tube.
Tobias JD et al[13]	1 (19 yr)	Renal transplantation	Intraoperative cardiac arrest with ongoing cardiovascular dysfunction. Had intra-aortic balloon pump (IABP) placed to provide cardiovascular stability. Coagulopathy, unresponsive to 5 units FFP, when it was time to remove IABP. PT decreased from 19.8 to 12.5 seconds and the INR decreased from 2.2 to 0.9 following 2.4 mg of rFVIIa. The IABP was removed without problems with local bleeding.
Morenski JD et al[14]	3 (5 wk, 20 mo, 1 yr)	Cerebral injury	Recombinant factor VIIa administered to control coagulopathy prior to placement of invasive intracerebral device for drainage of CSF or measurement of ICP.

IABP = intra-aortic balloon pump; CSF = cerebrospinal fluid; ICP = intracranial pressure