

Theme Issue Article

The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics

A systematic review

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Summary

From its original envisioned use in patients with hemophilia and inhibitors, recombinant factor VIIa has been increasingly used in a variety of non-hemophilia bleeding/hemorrhagic situations with great efficacy. Most of the reported work has been in adult patients. This paper sets out to review its use in the pediatric non-hemophilia patients and the varied conditions it has been

tried and used. Most of the published literature has shown that this agent is efficacious, safe and can be used as an adjunctive measure in the achievement of hemostasis. However, most of the published work is mainly anecdotal, case reports or small series. Randomized trials in children are eagerly awaited.

Keywords

rFVIIa, children, non-hemophilia bleeding

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Introduction

Recombinant factor VIIa (rFVIIa) was originally envisioned for the treatment of hemophilia patients with factor VIII or IX inhibitors. In fact, in the USA, this is the only FDA approved indication for this hemostatic agent. Since then, its role as a unique clotting factor substitute in many clinical non-hemophilia situations associated with bleeding has increased dramatically over the past few years as evidenced by the exponential increase of publications in this field. The term “universal hemostatic agent” is often used when describing the role of rFVIIa in various bleeding situations (1). These situations would include patients with congenital factor VII deficiency, hepatic failure, liver transplantation, prior to invasive procedures, upper gastrointestinal (GI) bleeding, cardiac surgery, abdominal and thoracic surgery, preterm infants, coagulopathy from various causes, qualitative and quantitative platelet disorders and trauma.

Based on studies in patients with hemophilia, Shapiro et al. have shown in a randomized trial that 90 µg/kg of rFVIIa every two hours was highly effective in achieving hemostasis in both, minor and major surgeries (2). Hemostasis was achieved in > 90% of patients during the first 48 hours. Statistically significant difference in efficacy from day 3 to day 5 was in favor of the high-dose rFVIIa (90 µg/kg) group across categories as compared to the lower dose of 35 µg/kg dose. However, optimal dose and schedule in other situations have not been completely resolved. Hence there is no consensus as to the appropriate dose and dosing schedule in non-hemophilia related bleeding situations.

Most of the published literature in the use of rFVIIa in non-hemophilia situations have been in adults. We set out to review specifically the role of rFVIIa in children (ages 0 to 20 years), and evaluate its efficacy in the pediatric population in the non-hemophilia setting. One of the main intent of this paper

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was also to provide a ready reference to clinicians who may be faced with a similar clinical scenario. This stemmed out of the need for providing information in one place (due to lack of one), as well as setting the stage for randomized clinical studies in children due to a dearth of these studies in this population.

Methods

The medical literature was searched for publications citing clinical experiences with rFVIIa, by using key index terms such as rFVIIa, factor VIIa, recombinant activated factor VII, children, pediatric patients, and NovoSeven®. Databases included Medline, Biosis, Embase, Medscape, and Current Contents. Searches covered the period from 1980 – August 2003. Only published manuscripts were selected. Abstracts and conference proceedings were not included. The papers were also evaluated for level of evidence i.e. randomized controlled trials (high-level), case series and non-controlled trials (mid-level) and case reports (low-level). The following caveats were considered with regards to data interpretation: publication bias (i.e. publication of positive results vs. non-publication of negative results), and whether the reports were uncontrolled studies vs. open label study vs. retrospective studies.

The following definitions were used for interpretation of data: efficacy (as defined by the authors) – for treatment that resulted in stopping of bleeding, treatment was successful, hemostasis was achieved, treatment was effective, treatment was good or excellent, or however else the authors defined a successful outcome; no underlying bleeding disorder – refers to patients who were bleeding but had no disorder making them susceptible to bleeding; adverse events – related to events that occurred in patients after administration of rFVIIa.

Results

Review of the published literature revealed that from 1988 to 2003, rFVIIa was used at least in 1030 patients (adults and pediatrics) in over 170 articles. There were 919 patients with an underlying bleeding disorder (659 hemophilia patients, 132 with liver disease, 45 with thrombocytopenia/thrombocytopenia, 77 patients were on anticoagulation, 4 were status-post bone marrow transplantation and 2 patients had uremia). There were 73 articles involving 659 hemophilia patients with 2836 bleeding events. The overall efficacy of rFVIIa as reported in this group of patients was 82%, while serious adverse events related to use of rFVIIa occurred in <1% of patients.

There were 63 articles reporting other coagulopathies in 260 patients. rFVIIa demonstrated an efficacy rate of 96% in 132 patients with liver disease (23 articles), 80% in 45 patients with thrombocytopenia/thrombocytopenia (21 articles) and 100% efficacy in 77 patients being treated with anticoagulation such as warfarin (15 articles). There were 111 patients with no

underlying bleeding disorder (40 articles). rFVIIa was determined to be effective in 93% of patients and to have a serious adverse event in 2% of them. Of these there were about 35 articles involving children <20 years of age. Eighteen of these were in children with an underlying coagulopathy other than hemophilia A or B, and 17 of these were reports of use in children with no previous underlying coagulopathy. This report will focus on these patients and describe them in each category, providing some details of the clinical scenarios which prompted the use of rFVIIa in these non-FDA approved situations.

Use in congenital Factor VII deficiency

In this category, there was one paper with mid-level (case series) evidence and two with low-level (anecdotal) of evidence. Given these data, it appears that a lower dose of rFVIIa is all that may be required in these cases to achieve hemostasis.

Mariani reported on 7 patients (ages 0.1-5 years) with severe factor VII deficiency, among a total of 17 patients including adults, who were treated with rFVIIa for 27 spontaneous bleeding episodes, 7 major and 13 minor surgical interventions (3). These patients presented with gum bleeding, hemarthroses, head trauma, or needed surgical interventions for tonsillectomy, dental extraction, retroperitoneal bleed, catheter insertion/removal, central nervous system (CNS) bleeding, craniotomy and inguinal herniotomy. The authors noted that a mean dose of 22-26 µg/kg of rFVIIa was found to be sufficient in all patients for effective hemostasis in these situations. The number of doses used ranged from 30-112. Only one patient (a 2 week old baby treated for an intracranial hemorrhage) developed antibodies 4-5 weeks after an extremely high dose (40 times higher than the average dose). All the others tolerated the therapy well without any adverse events.

There were two case reports – one by Wong et al., who reported on the use of rFVIIa in the treatment of massive intracranial hemorrhage in a neonate with severe FVII deficiency (FVII:c at 0%)(4) and the other one was by Billio et al., who reported the prophylactic use of rFVIIa in a 13 year old girl with severe congenital factor VII deficiency (FVII:c <1%) for multiple teeth extractions (5). In the former case, rFVIIa was administered every 4 hours at each of three dose levels: 15, 22 and 30 µg/kg with peak FVII:c levels of >100% after each infusion and mean trough levels above 25% for all three dose levels. There was no evidence of hypercoagulation by laboratory parameters, the infant tolerated rFVIIa well and maintained effective hemostasis with good clinical outcome. In the latter case, a dose of 24 µg/kg was used before the dental surgery with a repeat dose 7 hours later. Thereafter, two doses of 12 µg/kg were administered at 6-hour intervals. Local administration of tranexamic acid (4.8% solution) as a mouth wash was also used every 6 hours until suture removal. No bleeding was observed

during or after the procedure and at the time of suture removal. The patient also tolerated this therapy well (5).

Use in liver disorders

In this category, there were no high-level evidence papers. All were either small case series or case reports. All papers included children with liver failure and varying doses of rFVIIa were used as a last attempt to correct the coagulopathy or as preemptive therapy.

Hepatic failure

Brown et al. reported on 15 children (age 16 days -14 years, median 5 months) who were treated with rFVIIa for coagulopathy caused by liver failure from varying etiologies (6). Ten of these patients had acute liver failure and 5 had chronic liver failure with acute decompensation. All had prolonged prothrombin time (PT). Seven received rFVIIa therapy for clinical bleeding (GI or ostomy bleeds, severe epistaxis, recurrent oozing from central venous sites and visible blood in endotracheal tube secretions) despite maximal therapy with fresh frozen plasma (FFP) and platelet transfusions; the other 8 received rFVIIa as preemptive therapy. The dose of rFVIIa used was 80 $\mu\text{g}/\text{kg}$, with a median of 6 doses (decided on a case by case basis). The PT was corrected in all pts; 5 of the 7 bleeding patients had subjective improvement, with either cessation or slowing of their bleeding, and decrease in requirement for FFP and platelets. There was no appreciable benefit in reducing transfusion of PRBCs (packed red blood cells). Seven of the 15 patients were survivors (6 after an orthotopic liver transplant). There were no clinically detected episodes of thromboses attributed to rFVIIa therapy. Autopsies on three of the patients who died from other causes, did not show evidence of thromboses or infarcts or thrombotic compromise of the hepatic vasculature (6).

Chuansumrit et al. reported on three children with hepatic failure and disseminated intravascular coagulation (DIC) with overt clinical bleeding: two girls (age 3, 6 years) with dengue fever, one boy (age 9 months) was status-post hepatectomy (60% of liver removed). Case 1 had profound epistaxis and bleeding from the endotracheal tube, peritoneal dialysis and bilateral chest drains; case 2 had excessive bleeding from the GI tract and case 3 had bleeding from the operation drain. Cases 1 and 2 received rFVIIa plus other blood components; case 3 received rFVIIa as the sole hemostatic agent. They received a bolus of 40–90 $\mu\text{g}/\text{kg}$ followed by continuous infusion of 16.5–33 $\mu\text{g}/\text{kg}/\text{hr}$; infusion continued for 18, 40, 72 hours respectively, resulting in cessation of clinical bleeding. No adverse events related to the use of rFVIIa was reported (7).

Fulminant liver failure and hepatic transplantation

Kalicinski et al. described two children (2.5 yrs and 6 yrs of age) who had fulminant liver failure (International normalized ratios (INR) of 5.7 and 6.9 respectively) from non A non B hepatitis who were treated with rFVIIa (100 $\mu\text{g}/\text{kg}$) prior to liver transplantation (8). The liver transplants were successfully completed in both patients. There were no postoperative bleeding or thromboembolic complications in either patient (8).

Procedures in patients with liver failure

Chuansumrit et al. described five children with liver failure and associated coagulopathy who underwent surgical procedures under rFVIIa cover (9). The procedures included upper endoscopy for hematemesis in three patients, and liver biopsy in two patients. All received FFP pre-procedure, but still had prolonged PT. A dose of 40 $\mu\text{g}/\text{kg}$ of rFVIIa normalized PT in all and the procedures were completed without incident. One patient received 40 $\mu\text{g}/\text{kg}$ of rFVIIa every 6 hrs \times 48 hrs for ongoing GI bleeding.

Similarly, Young and Nugent described three infants with fulminant liver failure and associated coagulopathy, who underwent open liver biopsy (all 3 patients), and central venous line (CVL) placement in two, using a dose of 100 $\mu\text{g}/\text{kg}$ (10). Tobias and Berkenbosch described an 11-month-old infant with hepatic dysfunction related to total parenteral nutrition (TPN-induced cholestasis) and chronic coagulopathy who developed an upper GI bleeding from esophageal varices (11). Despite administration of FFP, bleeding persisted. Hence rFVIIa was used at a dose of 90 $\mu\text{g}/\text{kg}$. Coagulation parameters normalized and the GI bleeding subsided. No adverse events related to the use of rFVIIa were reported in any of these cases.

Use after cardiac surgery

No high-level evidence papers exist in this category. All were low-level evidence (case reports) papers.

The use of rFVIIa in the postoperative period after cardiac surgery was reported in four cases. In the pediatric case described by Al Douri et al. a 2.5 year old boy underwent arterial switch and ASD (atrial septal defect) closure, but suffered excessive intraoperative blood loss. Despite replacement, bleeding persisted. One dose of rFVIIa (30 $\mu\text{g}/\text{kg}$) resulted in cessation of bleeding, and an uneventful postoperative course (12). Similarly, Tobias et al. reported on a 4-month-old infant status-post an ASD repair, who in the postoperative period developed increasing sanguineous output from the chest tubes. Following a dose of rFVIIa (70 $\mu\text{g}/\text{kg}$), the coagulation parameters normalized with subsequent reduction in chest tube output. rFVIIa was also used in the same dose on postoperative day 7 to remove the transthoracic pulmonary artery catheter and the patient made an uneventful recovery (13). Two case reports from Israel using rFVIIa to control postoperative bleeding after

cardiac surgery was reported in a 10 week old girl with Down syndrome and a 6 year old boy with Job syndrome, with an uneventful outcome. The dose used was 90 $\mu\text{g}/\text{kg}$ – 100 $\mu\text{g}/\text{kg}$ (14, 15). No thrombotic complications were reported in either case.

Use in preterm/term infants

In this category, there were no high-level evidence papers; there was one mid-level evidence and a few low-level evidence reports.

In a study to estimate the effects of rFVIIa on PT in preterm infants, Griesen et al. studied two groups of preterm infants (16). These infants were between 25-32 weeks of gestation (median 28 weeks), age 6-69 hrs. In the first group (Study A), a dose escalation of the dose of rFVIIa was planned, starting at 5 $\mu\text{g}/\text{kg}$, then increasing to 10, 20, 40 or 80 $\mu\text{g}/\text{kg}$. Five infants were given 5 $\mu\text{g}/\text{kg}$ of rFVIIa. Their pre-rFVIIa PT ranged between 53-79 sec which decreased to 39-56 sec one hour after rFVIIa; no adverse events were reported. Subsequent dose escalation to 80 $\mu\text{g}/\text{kg}$ were carried out in the same babies whenever the PT was above 48 sec without any adverse effects. In Study B, the infants were randomized between 10 ml/kg of FFP vs. 80 $\mu\text{g}/\text{kg}$ rFVIIa. Four infants received FFP; their pre-FFP PT ranged from 53-92 sec; post-FFP their PT ranged from 40-59 sec. Seven infants received rFVIIa. Their pre-rFVIIa PT ranged between 53-92 sec; following treatment with rFVIIa their PT had decreased to 21-42 sec, which was significant as compared to those receiving FFP ($p=0.02$). PT remained lower in the rFVIIa group ($p=0.01$) at 3 hours than in the FFP group, whereas at 6 and 12 hours the differences were statistically insignificant. The authors estimated that the half-life of rFVIIa in these preterm infants were of the order of 2-3 hours. No adverse events were reported in those receiving rFVIIa. According to the authors, the study was too small to evaluate any hemostatic effects (16).

Veldman reported on the use of rFVIIa in two preterm infants (17). One was a 550 gram, 27 week infant, who on Day # 24 of life was taken to the operating room for repair of a sigmoid perforation. In the postoperative period, he developed critical bleeding from the liver and spleen and had a PT/aPTT of 49/61sec. Persistence of bleeding despite surgical attempts and replacement with blood products prompted the use of rFVIIa in a “desperate attempt” at a dose of 150 $\mu\text{g}/\text{kg}$ initially and another dose of 200 $\mu\text{g}/\text{kg}$ later, which resulted in cessation of bleeding. No clinical thromboembolic complications were found in the postoperative period. However, the patient died of multi-organ failure 13 days after the intervention. Autopsy was not done on this patient. The second was a 1320 gram, 28 week gestation infant, who developed postoperative bleed after a PDA (patent ductus arteriosus) ligation. This patient was given 200 $\mu\text{g}/\text{kg}$ of rFVIIa x 2 with immediate cessation of bleeding. No thrombotic complications were reported and the patient was

discharged home after a prolonged stay in the Neonatal Intensive Care Unit (NICU).

Chuansumrit et al. reported on a 1120 gram, 29-week pre-term infant, who developed bleeding from the umbilical stump with resultant hypotension and abdominal distention at 22 hours of age (18). At laparotomy, intra-abdominal bleeding was observed from a ruptured umbilical artery. By 63 hours of age, he had received 171 ml/kg PRBC, 103 ml/kg FFP, 7 ml/kg cryoprecipitate, and 67 ml/kg platelets without much success in achieving hemostasis. A single dose of 40 $\mu\text{g}/\text{kg}$ of rFVIIa resulted in cessation of bleeding from the umbilicus, surgical site, and ET tube. A repeat dose of rFVIIa at 70 hours was also given and the patient made an uneventful recovery.

Oloму et al. reported on two very low birth weight infants who received rFVIIa for severe pulmonary hemorrhage (19). The first, a 679 gram 27-week gestation infant, who developed severe bleeding from the endotracheal tube (ET) that failed to resolve despite PRBCs, platelets and FFP, received rFVIIa at 50 $\mu\text{g}/\text{kg}$ twice daily three hours apart for three consecutive days with cessation of bleeding. This infant made an uneventful recovery. The second, a 625 gram 24-week gestation infant, developed severe bleeding from the ET and received rFVIIa at a dose of 50 $\mu\text{g}/\text{kg}$ every three hours for 48 hours after failure to control bleeding with PRBCs, platelets and FFP, with resultant cessation of bleeding. This infant also made an uneventful recovery.

Use in qualitative platelet disorders

In this category there were no high-level evidence reports. Mid-level evidence and case reports were found.

Glanzmann Thrombasthenia (GT)

Tengborn first reported the use of rFVIIa in the management of a patient with GT (20). This was a two year old child with intractable epistaxis for whom rFVIIa was administered to control the bleeding. The dose used was 110 $\mu\text{g}/\text{kg}$ every 1.5 hrs initially; the interval was then increased to 2 hrs, then 3 hrs; hemostasis was achieved 3 hrs after the first dose; treatment was continued for 4–5 days, and the patient was discharged in good condition.

In an open label evaluation of rFVIIa, Poon et al. reported its use in 4 children with GT in 24 bleeding episodes after failure of local measures: nosebleeds (13), oropharyngeal bleeding (7), GI bleeding (3), facial bleeding (1), and one was used as prophylaxis during herniorrhaphy. rFVIIa (89 to 116 $\mu\text{g}/\text{kg}$) was used every 2 hrs until bleeding stopped, along with anti-fibrinolytics. The number of doses required to stop bleeding ranged from 1 -25. Hemostasis was achieved in 67% at 6 hrs, and 96% at 24 hrs. Platelet transfusion was required in 1 case (with a persistent GI bleed despite 24 rFVIIa doses over 2 days). Bleeding recurred in 2 other patients – one with a GI bleed that rebled 36 hours later, and one with a lip/frenulum cut that rebled

63 hours after initial treatment. The former was controlled by retreatment with 6 additional doses of rFVIIa, and the latter with 4 additional doses. No adverse effects of rFVIIa were observed (21).

Ancliff reported on the use of rFVIIa in an 18 month female patient with GT, who required insertion of a Port-a-cath for venous access. Along with platelet transfusions and tranexamic acid, she received 4 doses of 1.2 mg (approximately 120 µg/kg) rFVIIa, with one dose being given preoperatively, and the rest given at 90 minute intervals following the first. She tolerated the procedure well without excessive bleeding or complications (22). Ameri and Stolte reported using rFVIIa for a 10 year old with GT and platelet alloantibodies to GPIIb-IIIa for tonsillar bleeding. The patient received 300 µg/kg at 12 hour intervals until clinical cessation of bleeding (total 3 doses) (23). Chuansumrit et al. reported on 2 children with GT undergoing invasive dental procedures. rFVIIa at a dose of 180 – 200 µg/kg along with local measures including fibrin glue, mouth rinse with tranexamic acid, was successful in both cases. No excessive bleeding or complications were reported in either case (24). Devecioglu et al. described a 9 year old boy with GT, who presented in hypovolemic shock due to severe hematuria and was found to have a stone in the pelvis of his left kidney. Due to development of alloantibodies after platelet transfusion, rFVIIa was used (100 µg/kg) for a pyelolithotomy, both in the preoperative and postoperative period every two hours for three days. The surgery was performed without any major bleeding complications. The patient also received two platelet transfusions, one in the immediate preoperative period, and one in the immediate postoperative period, despite previous history of refractoriness to platelet transfusions. No thrombotic complications were reported (25). Caglar et al. reported on two patients with GT – a 5 year old boy and a 6 year old girl, both of whom were treated for severe epistaxis with rFVIIa after failure of platelet transfusions to control the bleeding, along with local measures. The five year old received 120 µg/kg for about 12 doses every three hours, then 75 µg/kg for three doses, following which there was cessation of bleeding. The 6 year old received 2 doses at 90 µg/kg with cessation of bleeding. No complications were reported with the use of rFVIIa (26).

In contrast to the above reports of success, Almeida et al. reported on the use of rFVIIa for 33 episodes (28 acute bleeding episodes of which 20 were from epistaxis, and 5 surgical interventions) in seven children with inherited platelet function disorders (5 with GT). The dose of rFVIIa used was mainly 100 µg/kg (1-3 doses), with 200 µg/kg used in 3 occasions. Those with GT had variable responses to rFVIIa. In 9 of 10 severe bleeding episodes (9 epistaxis, one menstrual bleed), the response was poor or ineffective. In 9 of 15 (60%) mild bleeding episodes, the response was excellent; presentation >12 hours from onset of bleeding was an unfavorable feature in achieving hemostasis (only 3 of 12 having an excellent or good

response as compared to 11/15 bleeding episodes presenting within 12 hours of bleeding). The site of bleeding also had some effect on response with only 40% of those with epistaxis responding as compared to a 72% response rate in those from bleeding from other sites. All 5 surgical procedures performed under the cover of rFVIIa had an excellent response and did not have any excess bleeding. Despite good results in mild bleeding episodes and 1/10 severe case, there was no overall reduction in transfusion requirements after use of rFVIIa in these patients (27)

Bernard-Soulier Syndrome (BSS) and other thrombocytopathies

Peters reported on a 5-year-old boy with BSS, who presented in hypovolemic shock due to severe epistaxis (Hgb decreased to 3.4 mM/I). There was no response to standard therapy. The patient received PRBCs, tranexamic acid and local packing. To prevent further bleeding, rFVIIa was used (77 µg/kg) every 4 hours for 24 hours; prompt hemostasis was achieved and he was discharged home in good condition (28). Almeida et al. reported on the use of rFVIIa for 5 episodes of bleeding (3 acute bleeding episodes, 2 for surgery) in 2 patients (1 each with BSS and storage pool disease - SPD). The dose of rFVIIa used was 100 µg/kg (2-4 doses). Both patients responded well to these doses. None required any transfusions of platelets or PRBCs and no adverse events were reported. (27).

Use in Type III vWD

Only a single case report exists in this category. Ciavarella et al. reported on two patients (a 15 year old and a 23 year old) with a vWF inhibitor titer of 3 u/ml and 48 u/ml, who received rFVIIa for dental procedures. Both these patients had developed immune/allergic reactions to vWF concentrates in the past. The pediatric patient received rFVIIa at a dose of 150 µg/kg for three doses every two hours, and then 200 µg/kg every two hours for 9 doses, then 90 µg/kg every two hours till the end of treatment. These doses were combined with tranexamic acid and local hemostatic agents (fibrin glue). No thrombotic complications were reported (29)

Use in uremic bleeding

Only one case report is recorded in this category. Revesz et al. reported on a 12 year old girl, status post-unilateral kidney transplantation, who developed severe cytomegalovirus pneumonitis requiring intubation (30). She also developed pulmonary hemorrhage secondary to uremic platelet dysfunction. Initial control was achieved with platelet and RBC transfusions. She developed rebleeding 3 days later and hence was treated with rFVIIa (90 µg/kg), resulting in prompt cessation of bleeding. The bleeding time decreased from ≥15 min to 6 min after treatment with rFVIIa. No adverse events were reported.

Use in trauma

The first report of the use of rFVIIa in trauma was from Israel, in a 19-year-old soldier admitted with a rifle injury where the bullet had torn through the inferior vena cava (IVC) at L5 with damage to the paravertebral muscles (31). The soldier was in hypovolemic shock, ketoacidosis, hypothermia, and had evidence of DIC. Replacement with blood products and surgical attempts to correct the underlying hemostatic disorder were unsuccessful. In a “desperate attempt” to control bleeding, rFVIIa at a dose of 60 µg/kg was administered. Coagulation improved markedly, and the rate of bleeding slowed down. The dose was repeated an hour later, and the oozing stopped immediately. There was no further blood loss, and patient remained stable and recovered clinically.

After this first successful case of use of rFVIIa in trauma, and a randomized, controlled safety and efficacy study on 10 hypothermic, coagulopathic swine with grade V liver injury supporting the hypothesis of the local effect of rFVIIa (32), the Ethical committee of the Israeli Ministry of Health approved the compassionate use of rFVIIa for patients suffering massive life-threatening bleeding from trauma. A total of 19 critically ill, coagulopathic, acidotic, hypothermic and multi-transfused cases with trauma were reported by Martinowitz et al. after this approval (33, 34). The ages of these patients ranged from 25 ± 17 years. Individual patient ages were not reported, but pediatric patients were also included in the report. All were treated with rFVIIa after all conventional hemostatic measures had failed. Hemorrhaging ceased after 1- 3 doses of rFVIIa within minutes in 15/19 (79%) patients. The total dose of rFVIIa required to control bleeding was 195 ± 112.7 µg/kg. Four patients did not respond to rFVIIa, one patient developed clinical deep vein thromboses, and two patients died after one week - one from sepsis and one from multi-organ failure. No autopsies were performed on the fatal cases. Thirteen patients (68%) survived and recovered.

Tobias et al. reported on three patients (ages 20 months, 11 years and 5 weeks) with closed head injuries who suffered severe coagulopathy after cerebral injury. One of them was given rFVIIa (90 µg/kg) after repeated doses of FFP failed to correct the coagulopathy, whereas the other two patients received rFVIIa as initial therapy. The first patient died despite attempts to control the raised intracranial pressure, whereas the other two were survivors (35).

Other reports in various conditions

Tobias et al. reported their experience in 10 children at their institution (36). The age of these patients ranged from 3 months to 19 years and their weight ranged from 3.7 to 49 kg. The dose of rFVIIa used ranged from 50 to 100 µg/kg, and the total number of doses used was 22. Clinical indication for the use included: active bleeding (17), prior to a procedure (3 – placement of intracranial pressure (ICP) monitor, Pericardial drain

and Central line placement), and removal of an invasive device (2 – removal of a transthoracic pulmonary artery line, and removal of an intra-arterial balloon pump). Indications for use of rFVIIa included coagulopathy showing no response to FFP, where time was a limiting factor, presence of life-threatening bleeding, unavailability of specific blood type, patient needing an immediate procedure, issues related to volume and hemodynamic effects of FFP, and/or religious objections (patients who were Jehovah’s witnesses). The etiology for the coagulopathy included: dilution coagulopathy in four patients, three of whom developed this after large volume transfusion during/following posterior spinal fusion surgery, and one was status post-cardiopulmonary bypass. Four patients had evidence of DIC, two after sustaining head trauma, and one each after sepsis/shock and status-post cardiac arrest, respectively. Two patients had evidence of hepatic insufficiency, one secondary to cystic fibrosis, and one from TPN cholestasis. All these children had a favorable response to rFVIIa with improvement in their clinical condition and no adverse effects related to the use of rFVIIa (36).

Park et al. reported on 3 pediatric patients (ages 5 months, 8 years and 17 years), who received rFVIIa (dose ranging from 40 – 90 µg/kg) for the rapid correction of coagulopathy prior to neurosurgical procedures. The younger two patients underwent craniotomy for draining of epidural hematomas, while the oldest one had an ICP monitor placed for Grade IV encephalopathy secondary to end-stage liver disease. None developed any procedure-related complications. All patients received FFP prior to rFVIIa except the 8 year old who needed an emergency craniotomy that could not wait for the delay in obtaining FFP (37).

The author’s experience with use of rFVIIa in non-hemophilia situations include seven patients, 4 of which were published (38). These included a 15 year old female with GT who underwent successful dental extraction and dental cleaning using 3 doses of rFVIIa (90 µg/kg), a 2.5 year old boy with hepatoblastoma, status-post chemotherapy and hepatic lobectomy, who received 25–30 µg/kg of FVIIa every 12 hours for three days for postoperative bleeding from the surgical site and to prevent fluid overload in the post-operative period; a 3 year old boy with acute myeloid leukemia who developed non-overt DIC during his first cycle of chemotherapy received two doses of 25 µg/kg of rFVIIa 12 hours apart; and an 8 day old male child received 2 doses of rFVIIa at a dose of 25 µg/kg for treatment of postoperative bleeding after repair of a congenital heart defect. No adverse events were seen in any of the patients, and all patients had evidence of successful hemostasis with use of rFVIIa.

Discussion

This report describes the varied clinical scenarios where rFVIIa was used and found to be efficacious and safe. Would these conditions be appropriate indications for the use of rFVIIa? It seems to have worked in these situations. However, it is impossible to claim or calculate the efficacy and safety data from these reports as there may be a serious reporting bias, i.e. failures of treatment or serious (especially fatal) adverse events of the off-label use, and even written contraindications (e.g. DIC) is unlikely to be reported or published. Additionally, commercial virally inactivated plasma derived FVII is available in some countries and may be used for patients, especially those with congenital factor VII deficiency. This may be more physiological in this situation and can be better monitored. Recently, rFVIIa was approved in the European Union (EU) for congenital factor VII deficiency and Glanzmann Thrombasthenia with alloantibodies. What can we conclude from these reports? See Table 1 for a summary of the dosing and indications as reported.

Advantages of rFVIIa in emergency / “desperate” situations

rFVIIa has a rapid onset (10 minutes), and works as a general hemostatic agent with low risk of thrombogenicity in this population; additionally, its low volume leads to rapid administration without risk of fluid overload especially in the postoperative setting; it has a short preparation time, does not require thawing unlike FFP, and has had no reports of anaphylactic reactions. Being a recombinant product, there are no infectious disease issues to be concerned about, as compared to FFP and other blood products (36, 39, 40). Additionally, these children tolerated the drug without any major adverse events.

Disadvantages of rFVIIa

Though none of the papers reported major adverse events or the economics of using this medication, it needs to be stated that there are disadvantages of using this product – its short half life in children (about 2 hours) which translates to frequent dosing and therefore increased costs. At our institution, the cost of using this product is about a \$1/μg. Additionally, we have limited or no high-level evidence-based data on efficacy in non-hemophilia situations, limited safety data, limited data on dosing outside of the hemophilia arena and the theoretical risk of increased thromboembolic complications. There have been reports of thromboembolic events in the adult population, though in most of them, predisposing factors such as previous cardiovascular disease and advanced age were present. Moreover, as noted (vide supra) in these reports, rFVIIa may not be effective in all cases (e.g. epistaxis in patients with GT). There are no good ways of monitoring the efficacy of this product. Most of the reports used the shortening of the PT to monitor its effect. However, it must be emphasized that this does not completely reflect the *in vivo* effect of rFVIIa on the coagulation process and therefore may not be a useful parameter for monitoring (39, 41).

What can we learn from these reports

rFVIIa was used in the majority of the patients reported after standard care failed to achieve adequate hemostatic control – “in a desperate attempt”. It was successful in the majority of situations in saving lives. Since no prospective studies are available, standard care must be used first, before rFVIIa is used in these non-approved settings. The bolus dosing of rFVIIa used varied from as low as 15 μg/kg in congenital factor VII deficiency to as high as 300 μg/kg in other situations, at intervals varying from 1.5 hours to every three hours to every 12 hours. Single to multiple doses were used to achieve hemo-

Table 1: Summary of dosing and indications in published reports.

μg/kg	Indication	Responses	Comments
Low Dose (<35)	1. Congenital Factor VII deficiency 2. Postop heart 3. Preterm infants 4. Non-overt DIC	All patients had a hemostatic response; No adverse events reported using rFVIIa	rFVIIa given after failure of other hemostatic agents or as preemptive therapy
Intermediate dose (35-90)	1. Liver disorders 2. Procedures in Liver failure 3. Postop heart 4. Preterm Infants 5. Bernard-Soulier 6. Uremic bleeding 7. Trauma 8. Neurosurgical procedures	All patients had a hemostatic response; No adverse events reported using rFVIIa	rFVIIa given after failure of other hemostatic agents or as preemptive therapy
High dose (>90)	1. Fulminant Liver failure – hepatic transplantation 2. Postop heart 3. Post surgery in Preterm Infants 4. Glanzmann Thrombasthenia 5. Type III vWD with Inhibitor 6. Trauma	All patients had a hemostatic response; No adverse events reported using rFVIIa	rFVIIa given after failure of other hemostatic agents or as preemptive therapy; Failure to control severe epistaxis in patients with Glanzmann in some reports.

stasis. There are also patients who do not respond to rFVIIa therapy, and the exact etiology of this or which patients fail to respond is unknown at this time.

Remaining questions

Many questions still remain unanswered at this time with regards to use of rFVIIa in non-hemophilia bleeding situations: we do not know the exact mechanism(s) of this effect and we do not know which dose is best in these conditions. Additionally, we do not know which clinical settings increase the risk of adverse effects, even though in post-marketing surveillance it has an excellent adverse event profile and a favorable risk-to-benefit ratio with very rare occurrence of thromboembolic events (NovoNordisk, Inc. personal communication). We still need ongoing safety data in children; we still do not know what platelet count is adequate, and what levels of other coagulation factors are adequate for its efficacy. Additionally, we do not know its safety in associated morbid conditions (e.g. post cardiac bypass grafting, other types of vascular anastomosis, patients with sepsis and multisystem organ failure syndromes, DIC), its efficacy with normal coagulation function and prophylactic administration in high blood loss surgery (36). Most importantly we still do not have a way to effectively monitor rFVIIa therapy and its efficacy. Until we know these answers and randomized studies have been conducted, rFVIIa will

remain an adjunctive therapy to be used after standard hemostatic therapy has failed.

Conclusions

The above reports suggest that rFVIIa can enhance hemostasis in patients with FVII deficiency, liver failure, trauma, coagulopathic conditions, thrombocytopathic conditions and surgery. Albeit case series and reports, these data show the safety and efficacy of rFVIIa in uncontrolled bleeding situations in children. Large randomized trials comparing rFVIIa and standard transfusion care is required to conclusively prove the efficacy and safety of rFVIIa in both the preventive and therapeutic use of this agent in bleeding situations in the pediatric non-hemophilia population.

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References

- Hedner U. Recombinant activated factor VII as a universal hemostatic agent. *Blood Coagul Fibrinolysis* 1998; 9: S147-52.
- Shapiro AD, Gilchrist GS, Hoots WK, et al. Prospective, randomized trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80: 773-8.
- Mariani G, Testa MG, Di Paolantonio T, et al. Use of recombinant activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sanguinis* 1999; 77: 131-6.
- Wong WY, Huang WC, Miller R, et al. Clinical efficacy and recovery levels of recombinant FVIIa (NovoSeven) in the treatment of intracranial haemorrhage in severe neonatal FVII deficiency. *Haemophilia* 2000; 6: 50-4.
- Billio A, Pescosta N, Rosanelli C, et al. Successful short term oral surgery prophylaxis with rFVIIa in severe congenital factor VII deficiency. *Blood Coagul Fibrinolysis* 1997; 8: 249-50.
- Brown JB, Emerick KM, Brown DL, et al. Recombinant factor VIIa improves coagulopathy caused by liver failure. *JPGN* 2003; 37: 268-72.
- Chuansumrit A, Chantarojanasiri T, Isarangkura P, et al. Recombinant factor VIIa in children with acute bleeding resulting from liver failure and DIC. *Blood Coagul Fibrinolysis* 2000; 11(suppl 1): S101-5.
- Kalickinski P, Kaminski A, Drewniak T, et al. Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. *Transplant Proc* 1999; 31: 378-9.
- Chuansumrit A, Treepongkaruna S, Phuapradit P. Combined fresh frozen plasma with recombinant factor VIIa in restoring hemostasis for invasive procedures in children with liver diseases. *Thromb Haemost* 2001; 85: 748-9.
- Young G, Nugent DJ. Prevention of bleeding complications in neonates with liver failure undergoing surgery using recombinant factor VIIa. *Hematology* 2001; 6: 341-6.
- Tobias JD, Berkenbosch JW. Synthetic factor VIIa concentrate to treat coagulopathy and gastrointestinal bleeding in an infant with end-stage liver disease. *Clin Pediatr* 2002; 41: 613-6.
- Al Douri M, Shafi T, Al Khudairi D, et al. Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coagul Fibrinolysis* 2000; 11(suppl 1): S121-S7.
- Tobias JD, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Ped Crit Care Med* 2003; 4: 49-51.
- Kenet G. rFVIIa for profuse bleeding in surgical patients. *Bloodline Rev* 2001; 1: 12-13.
- Leibovitch L, Kenet G, Mazor K, et al. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. *Ped Crit Care Med* 2003; 4: 444-6.
- Greisen G, Andreasen RB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. *Blood Coagul Fibrinolysis* 2003; 14: 117-20.
- Veldman A, Fischer D, Voight B, et al. Life-threatening hemorrhage in neonates: management with recombinant activated factor VII. *Intensive Care Med* 2002; 28: 1635-7.
- 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: 169-71.
- Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII in very low birth weight infants. *J Perinatol* 2002; 22: 672-4.

20. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost* 1996; 75: 981-2.
21. Poon MC, Demers C, Jobin F, et al. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann Thrombasthenia. *Blood* 1999; 94: 3951-3.
22. Ancliff P, Leisner R, Khair K, et al. The use of recombinant factor VIIa in a patient with severe Glanzmann's thrombasthenia to facilitate insertion of a Port-a-cath. *Blood Coagul Fibrinolysis* 1999; 10: 447-8.
23. Ameri A, Stolte S. Correlation of activated clotting time with rFVIIa infusion and clinical efficacy in a patient with Glanzmann Thrombasthenia and platelet alloantibodies. *Thromb Haemost* 2002; 87: 1084.
24. Chuansumrit A, Suwannuraks M, Sri-Udomporn N, et al. Recombinant activated factor VII combined with local measures in preventing bleeding from invasive dental procedures in patients with Glanzmann thrombasthenia. *Blood Coagul Fibrinolysis* 2003; 14: 187-90.
25. Devecioglu O, Unuvar A, Anak S, et al. Pyelolithomy in a patient with Glanzmann Thrombasthenia and antiglycoprotein IIb/IIIa antibodies: the shortest possible duration of treatment with recombinant activated factor VII and platelet transfusions. *Turk J Pediatr* 2003; 45: 64-6.
26. Caglar K, Cetinkaya A, Aytac S, et al. Use of recombinant factor VIIa for bleeding in children with Glanzmann thrombasthenia. *Pediatr Hematol Oncol* 2003; 20: 435-8.
27. Almeida AM, Khair K, Hann I, et al. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol* 2003; 121: 477-81.
28. Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier Syndrome and recurrent nosebleeds with recombinant factor VIIa. *Thromb Haemost* 1998; 80: 352.
29. Ciavarella N, Schiavoni M, Valenzano E, et al. Use of recombinant factor VIIa in the treatment of two patients with type III von Willebrand's disease and an inhibitor against the von Willebrand factor. *Haemostasis* 1996; 26: 150-4.
30. Revesz T, Arets B, Bierings M, et al. Recombinant factor VIIa in severe uremic bleeding. *Thromb Haemost* 1998; 80: 353.
31. Kenet G, Walden R, Eldad A, et al. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; 354: 1879.
32. Martinowitz U, Holcomb JB, Pusateri AE, et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with highgrade V liver injuries. *J Trauma* 2001; 50: 721-9.
33. Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001; 51: 431-9.
34. Martinowitz U, Kenet G, Lubetsky A, et al. Possible role of recombinant factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anesth* 2002; 49(10): S15-S20.
35. Morenski JD, Tobias JD, Jimenez DF. Recombinant activated factor VII for cerebral-induced coagulopathy in pediatric patients. *J Neurosurg* 2003; 98: 611-6.
36. Tobias JD, Groeper K, Berkenbosch. Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. *Southern Med J* 2003; 96: 12-6.
37. Park P, Fewel ME, Garton HJ, et al. Recombinant activated factor VII for the rapid correction of coagulopathy in non-hemophilic neurosurgical patients. *Neurosurgery* 2003; 53: 34-9.
38. Mathew P, Winter SS, Frost JD, et al. Novel applications of recombinant factor VIIa for management of pediatric coagulopathic diseases. *J Pediatr Hematol Oncol* 2003; 25: 499-502.
39. Lusher J, Ingerslev J, Roberts H, et al. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis* 1998; 9: 119-28.
40. Roberts HR, Monroe DM, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol* 2004; 41: 101-8.
41. Hedner U, Erhardtson E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002; 42:114-124.