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Clinical Investigation

Recombinant Factor VIIa for Bleeding in Non-hemophiliac Pediatric Patients

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OBJECTIVE To evaluate the use of recombinant factor VIIa (rFVIIa) for the treatment of bleeding in non-hemophiliac children.
METHODS This was a retrospective chart review of all patients < 18 years of age who received rFVIIa over a 2 year period.
RESULTS Twenty-four pediatric patients received a total of 240 doses of rFVIIa for treatment of bleeding. Recombinant factor VIIa was effective in achieving bleeding resolution in 54% of patients. The mean age of patients in the bleeding non-resolution versus resolution group was 50% younger (5.5 vs. 10.3 years, P = 0.104).
CONCLUSIONS Bleeding resolution can be achieved with recombinant factor VIIa using similar doses to those recommended for children with hemophilia. Widespread use of rFVIIa for bleeding in children without hemophilia is not warranted given this efficacy data. Further safety studies are needed with rFVIIa in this population to clarify thrombotic risks.

KEYWORDS children, factor VIIa, bleeding, hemophilia, non-hemophiliac

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INTRODUCTION

Recombinant factor VIIa (rFVIIa) is indicated for treatment and prevention of bleeding in hemophilia patients with inhibitors to factors VIII or IX and in patients with congenital factor VII deficiency.[1] Use of rFVIIa for other bleeding conditions has increased in recent years with demonstrated efficacy to control bleeding in a number of non-hemophilia coagulopathies in adults.[2-4]

Activated factor VII initiates coagulation tissue factor-dependent and independent pathways.[5-7] After vascular wall or tissue injury, factor VII in plasma binds to exposed tissue factor (TF) and activates factors IX and X leading to thrombin generation and subsequently fibrin clot formation.[5,8,9] Activated factor VII also directly activates factor X, independent of TF, by binding to activated platelets.[10]

Although less widely reported in pediatrics than adults, rFVIIa use for non-hemophiliac children with uncontrolled bleeding has been shown to be safe and effective.[11] Reports in children describe a number of conditions that may benefit from rFVIIa including bleeding related to cardiac surgery, liver failure and transplantation, platelet disorders, neurosurgery, and disseminated intravascular coagulation (DIC).[12-23] Current knowledge of coagulation function has helped broaden rFVIIa use for many of these indications, although data are still limited. The main objective of this study was to evaluate the

ABBREVIATIONS AERS, Administration's Adverse Event Reporting System; DIC, disseminated intravascular coagulation; FFP, frozen plasma; INR, international normalized ratio; PRBC, packed red blood cells; PT, prothrombin time; PPT, partial thromboplastin time; rFVIIa, recombinant factor VIIa; TF, tissue factor

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Table 1. Primary outcome definitions

Outcome	Definition
No Change from Baseline	No change in bleeding or blood product requirement when used as treatment for bleeding
Single Dose Bleeding Resolution	Resolution of bleeding after one dose
Multiple Dose Bleeding Resolution	Resolution of initial bleeding after two or more rFVIIa doses
Death	Bleeding-related
Death	Unrelated to bleeding

use, efficacy, and safety of rFVIIa for the treatment of bleeding in non-hemophiliac pediatric patients at a single tertiary care pediatric center.

METHODS

A retrospective chart review was conducted of all patients receiving recombinant activated factor VII (rFVIIa, NovoSeven; NovoNordisk, Copenhagen, Denmark) from June 2003 through July 2005 at Riley Hospital for Children, Indianapolis. All patients < 18 years old were included in analysis. Patients with hemophilia A and B, as well as patients receiving rFVIIa for prophylaxis, were excluded. The hospital Institutional Review Board approved this study.

Demographic data collected included age, gender, weight, length of hospitalization, Intensive Care Unit length of stay, primary prescribing service, and presence or absence of a hematology consultation. Clinical data obtained included underlying indication for rFVIIa, transfusion of fresh frozen plasma (FFP), packed red blood cells (PRBC), platelets, cryoprecipitate, and concomitant medications influencing coagulation. Laboratory data included the prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, fibrinogen level, factor VII activity, and d-dimer. All laboratory parameters from before and after (when available) rVIIa administration were recorded. Lastly, we recorded each individual dose (mcg/kg) and the total number or rFVIIa doses administered to each patient.

Indications for rFVIIa therapy were classified as bleeding from liver failure, DIC, gastrointestinal bleeding, post cardiac surgery, and other. The primary outcome of rFVIIa therapy was assessed through chart documentation with subsequent categorization of patients into one of the following five outcome groups: no change from baseline, bleeding resolution, additional rFVIIa dosing requirement with resolution, death associated with bleeding, and death from other causes. Primary outcomes are defined in Table 1.

Mean dosing for outcome groups (resolution versus no resolution) were compared using independent samples t-test. The Kruskal-Wallis test was used to examine the differences of mean doses for each treatment indication. A paired-sample t-test was used to compare PT, INR, and PTT values before and after rFVIIa dosing. Statistical significance was assumed with $P < 0.05$. Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 14.0 Chicago, Illinois) and are presented as mean ± SD.

RESULTS

Forty-eight patients received rFVIIa during the study period of June 2003 through July 2005. Figure 1 illustrates study patients included and excluded from analysis. Twenty-four children ranging in age from 2 days to 17 years (median: 5.5 years) and weight from 1.2 to 88 kg (mean: 33.1 kg) were included in analysis, and received a total of 240 doses of rFVIIa.

Treatment indications for rFVIIa included liver failure (n = 7, 29.2%), GI bleeding (n = 4, 16.7%), post cardiac surgery (n = 3, 12.5%), DIC (n = 3, 12.5%), and other (n = 7, 29.2%). Table 2 describes the characteristics of patients who received rFVIIa. Twenty-two (92.7%) patients received at least one transfusion of FFP, PRBC, platelets or cryoprecipitate.

The mean rFVIIa dose administered to all patients was 85.3 ± 20.1 mcg/kg. The mean doses used for the treatment indications of liver failure, GI bleeding, post-cardiac surgery, DIC, and others were 69.1, 88.9, 94.1, 89.9, and 89.5 mcg/kg, respectively, and were not significantly different ($P = 0.475$). However, the mean dose used for

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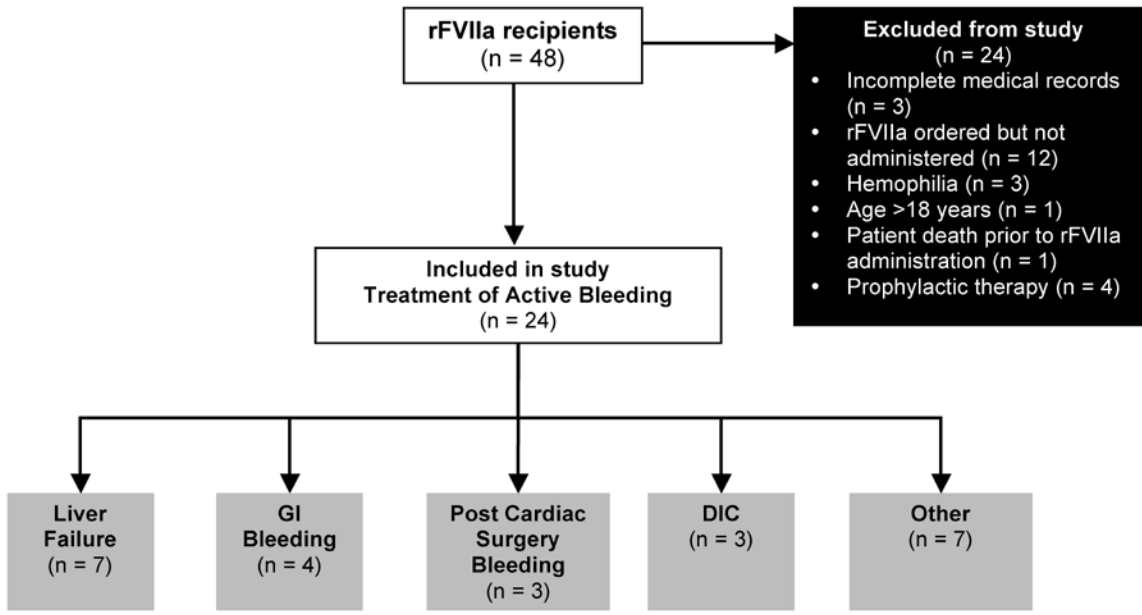

Figure. Patient Flow.

bleeding associated with liver failure (69.1 mcg/kg) was 19% lower that the mean dose administered to all patients.

Bleeding resolution occurred in 13 (54%) patients after an average of 10.8 doses (range 1-46). Comparing responders to non-responders, neither the mean dose (81.9 vs. 86.7 mcg/kg, P = 0.4) nor the mean number of doses (10.8 vs. 9.1, P = 0.209) were significantly different. Bleeding non-responders were 50% younger (5.5 vs. 10.3 years, P = 0.104) than responders. Nine deaths occurred, but none were directly attributable to bleeding. Patient outcomes are listed in Table 2.

Pre and post rFVIIa dosing laboratory values for PT, INR, and PTT were available for 25 (10.4%) of the 240 total doses. The mean PT and INR before and after rFVIIa decreased from 17.9 to 14.0 seconds (P = 0.04) and from 1.6 to 1.2 (P = 0.05), respectively. The mean PTT increased after rFVIIa dosing from 45.1 to 48.7 seconds (P = 0.71). One adverse event was documented in the 24 patients. This patient experienced a right femoral deep vein thrombosis following rFVIIa therapy. The patient was subsequently started on a heparin infusion with no additional bleeding problems. No additional adverse events were documented.

DISCUSSION

Factor VIIa plays an important role in the coagulation cascade. Due to its mechanism of action, recombinant FVIIa has the potential to be an effective hemostatic agent for a number of bleeding conditions unrelated to hemophilia. There are many case reports and small case series describing rFVIIa for bleeding conditions in non-hemophilic children. Also, several retrospective studies have been conducted but have yielded data in a relatively small number of children.[13,15,17,18,24-27] Only three prospective studies have been performed.[12,14,16] Table 3 summarizes published data pertinent to our study regarding the use of rFVIIa for treatment of active bleeding. Recombinant factor VIIa administration resulted in bleeding resolution in 54% of our patients. The percentage of patients with a positive response to rFVIIa is slightly lower than that published in other studies; although our study is considerably larger than previous works.

Pychynska-Pokorska and colleagues evaluated the efficacy of rFVIIa to control bleeding after cardiac surgery and cardiopulmonary bypass in eight children in a prospective open label study.[14] Recombinant factor VIIa use reduced post-operative blood loss, and resulted in cessation of bleeding in 7 of 8 patients after doses of 30–60 mcg/kg.[14] Two retrospective studies demonstrated that rFVIIa significantly reduced blood loss post cardiac surgery after doses of 56–180 mcg/kg.[15,25] All of our rFVIIa recipients after cardiac surgery

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Table 2. Characteristics of patients receiving recombinant factor VIIa therapy

Patient age (sex)	Indication	Outcome	Doses	Mean Dose (mcg/kg)
2 wks (M)	DIC	Additional rVIIa doses with resolution	30	89.9
16 yrs (F)	DIC	Additional rVIIa doses with resolution	46	90
6 yrs (F)	DIC	Bleeding resolution	1	90
12 yrs (M)	GI Bleeding	Death	14	52.4
2 yrs (M)	GI Bleeding	Death	5	103.4
17 yrs (M)	GI Bleeding	Death	2	98.9
5 yrs (F)	GI Bleeding	No change	1	75
2 wks (F)	Liver Failure	Additional rVIIa doses with resolution	19	44
16 yrs (M)	Liver Failure	Bleeding resolution	1	45
15 yrs (M)	Liver Failure	Death	4	54.5
1.4 yrs (M)	Liver Failure	Death	6	84.9
5 yrs (F)	Liver Failure	Death	31	92.3
1 day (M)	Liver Failure	Death	19	111.1
1.2 yrs (F)	Liver Failure	No change	5	51.7
15 yrs (M)	Circumcisional bleeding	Additional rVIIa doses with resolution	3	61.5
7 mo (F)	Familial hemophagocytic histiocytosis	Death	12	96.7
15 yrs (M)	Gross hematuria	Additional rVIIa doses with resolution	13	85.3
15 yrs (M)	Hemorrhagic cystitis	Additional rVIIa doses with resolution	2	90.9
1.5 yrs (M)	Subdural hematoma, history of ALL	Death	1	106.2
16 yrs (F)	Toxic epidermal necrosis secondary to lamotrigine	Additional rVIIa doses with resolution	17	96
11 mo (M)	Epistaxis refractory to standard therapy	Additional rVIIa doses with resolution	2	90
8 mo (F)	Post Cardiac Surgery	Additional rVIIa doses with resolution	4	109
16 yrs (M)	Post Cardiac Surgery	Bleeding resolution	1	75.3
17 yrs (M)	Post Cardiac Surgery	Bleeding resolution	1	116.9

F, female; M, male; ALL, acute lymphoblastic leukemia

had resolution of bleeding. However, we did not quantify blood loss in these patients in the time periods surrounding rFVIIa dosing.

Bleeding associated with liver failure and GI bleeding accounted for 46% of the rFVIIa usage in our population. Our observed efficacy for these patients was less than in published reports that have shown bleeding resolution occurring in 71%–100% of patients.[16,17,23,28-31] Brown and colleagues reported that 71% of patients with liver failure treated with rFVIIa (80 mcg/kg) for bleeding unresponsive to FFP and platelet transfusion had subjective improvement.[17] The seven patients with liver failure in our study received an average rFVIIa dose of 69 mcg/kg. Two (29%) of our patients with liver failure had resolution of bleeding, four (57%) patients died unrelated to bleeding, and one had no clinical change from baseline. Reports of rFVIIa use in GI bleeding show that 50% of patients experience resolution of bleeding.[23,29,30] Doses in these reports varied from 4–270 mcg/kg. One report described use of a continuous infusion of rFVIIa following initial boluses.[23] The average rFVIIa dose for GI bleeding in our patients was 88.9 mcg/kg, which is well within the range of other reports;however,

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no favorable responses were observed.

Older children tended to respond more favorably to rFVIIa dosing. The mean age of non-responders (5.5 years) in our treatment group was about half that of responders (10.3 years). This difference could relate to the differences in pharmacokinetics of rFVIIa in children versus adults. Villar and colleagues demonstrated that after 90 mcg/kg doses, children had lower plasma levels of rFVIIa than adults.[32] Children also have significantly faster clearance of rFVIIa than adults.[32,33] As the use of rFVIIa continues to increase in children without hemophilia, further pharmacokinetic and pharmacodynamic studies are needed to fully determine age-related differences.

Of concern was that one patient in our study developed a right femoral deep vein thrombosis after receiving rFVIIa. Only one other confirmed thrombotic adverse event attributable to rFVIIa has been reported in 138 children (0.7%).[12-18,25-27] The Food and Drug Administration's Adverse Event Reporting System (AERS) describes reports of 185 thromboembolic events following the use of rFVIIa.[34] It is difficult to compare the AERS data with available safety data from pediatrics due to the lack of quality exposure data and the voluntary reporting nature of the AERS. However, a review of controlled clinical trials of rFVIIa showed that the incidence of thromboembolic events in rFVIIa treated patients (6%) did not differ from placebo treated patients (5.3%).[35] Obviously, it is difficult to determine true incidence and risk of thromboembolic adverse events after rFVIIa given the limited number of controlled trials in children without hemophilia. Additional safety studies are warranted.

Formal guidelines for rFVIIa use at our institution were not in place during the study period. The rFVIIa indications and doses used in our study are consistent with previous reports, but that alone does not suggest that rFVIIa therapy was indicated or appropriate for each patient. Also, while this study was not designed to evaluate cost effectiveness, it is important to consider the drug-related expenditures along with the 54% efficacy. In the 24 patients in our study, drug costs for rFVIIa totaled approximately $797,000 with a median treatment course cost of approximately $10,700. Furthermore, 21 patients were primarily cared for by a service other than pediatric hematology, but only 43% of those had a hematology consultation to assist with the management of bleeding. Given the drug costs and overall bleeding resolution in our study, formal dosing guidelines that incorporate hematology consultation could be instituted to improve appropriateness and overall cost-efficiency.

Our sample size is relatively small, although it is one of the largest studies of recombinant activated factor VII in non-hemophiliac children. Additionally, our study was not designed to predict patient specific factors indicative of positive or negative response to rFVIIa. Therefore, we cannot conclude with certainty why 46% of our patients did not respond to rFVIIa, despite having received similar mean mcg/kg doses and mean quantity of doses as patients who did respond. Also, this study did not completely evaluate timing of rFVIIa administration in relation to the patient's clinical bleeding episode in order to correlate treatment outcome. Lastly, laboratory parameters such as PT, PTT, INR and fibrinogen levels were not consistently obtained, thus resulting in difficulties in analyzing normalization of laboratory values as an indicator of appropriate response.

CONCLUSIONS

This study presents additional data further describing the efficacy and safety of rFVIIa for bleeding unrelated to hemophilia in pediatric patients. Bleeding resolution for this population may be achieved using doses similar to those recommended for children with hemophilia. However, our results do not support the widespread use of rFVIIa for treatment of bleeding in non-hemophilia children. Hospital policies designed to guide practitioners towards appropriate use of rFVIIa should be considered. Based on the pharmacokinetics of recombinant factor VIIa and the observation that younger patients tended to not respond as well as older patients, additional research is needed to determine age-dependent variables that affect dosing requirements in non-hemophilic children. Prospective randomized controlled trials are needed to determine the role of rFVIIa in non-hemophilic children with significant bleeding and to further clarify its safety profile.

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Table 3. Summary of rFVIIa data for treatment of active bleeding non-hemophilic children

Reference	Study Design (patient numbers)	Age	Indication for rFVIIa	Dose (mcg/kg)	Outcome
Oen*	Retrospective (n = 24)	2 days-17 yrs	See Table 2	26-184	Bleeding resolution in 54% of patients
Brown[17]	Retrospective (n = 15)	16 days-14 yrs	Acute or chronic liver failure associated bleeding	80	Cessation or slowing of bleeding in 71% of patients
Pettersson[16]	Prospective (n = 22 episodes in 7 patients)	4 mo-10 yrs	Chronic liver failure associated bleeding	36-118	Bleeding resolution in 45% of episodes
Tobias[13]	Retrospective (n = 10)	3 mo-19 yrs	Coagulation disturbances secondary to DIC (4), hepatic insufficiency (2), post CPB (1), large-volume transfusion (3)	50-100	Correction of PT and INR after rFVIIa ($P < 0.001$); Correction of bleeding in 100% of patient
Pychynska-Pokorska[14]	Prospective (n = 8)	5 days-18 yrs	Excessive blood loss after CPB	30-60	Decreased blood loss at 1 hour after rFVIIa dosing ($P = 0.004$) in 88% of patients
Heisel[21]	Case Report (n = 8)	3 mo-17 yrs	Intraoperative bleeding during brain tumor resection	75-275	Hemostasis after one or more rFVIIa doses in 88% of patients
Tobias[27]	Retrospective (n = 9)	Mean = 9 yrs	Excessive blood loss after CPB	90 x 1	Decreased chest tube output 3 hours after rFVIIa dosing ($P = 0.0011$)
Egan[25]	Retrospective (n = 6)	0.5 mo-8 yrs	Blood loss associated with cardiac surgery	180	Bleeding resolution in 100% of patients Decreased blood loss after 2nd rFVIIa dose ($P = 0.004$)
Chuansumrit[36]	Case Series (n = 5)	2 mo-14 yrs	Liver disease related bleeding	40	Hemostasis achieved and PT corrected in 100% of patients
Razon[15]	Retrospective (n = 5)	3 days-19 yrs	Blood loss after cardiac surgery	56-96	Decreased blood loss and blood product requirement after rFVIIa dosing in 100% of patients
Atkison[28]	Case Report (n = 4)	3 mo-11 yrs	Liver failure related bleeding (4) and prior to liver biopsy (1)	67-300	Bleeding resolution in 100% of patients No bleeding occurred from liver biopsy
Mathew[37]	Case Report (n = 4)	8 days-15 yrs	DIC (2), Glanzmann thrombasthenia bleeding prevention after hepatic lobectomy (1)	25-90	Bleeding resolved or prevented in 100% of patients

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Table 3. Summary of rFVIIa data for treatment of active bleeding non-hemophilic children (cont.)

Reference	Study Design (patient numbers)	Age	Indication for rFVIIa	Dose (mcg/kg)	Outcome
Wittenstein[24]	Retrospective (n = 4)	6 days-33 mo	Bleeding during ECMO after cardiac surgery	90-120	Reduced blood loss after dosing (P = 0.025)
Chuansumrit[23]	Case Report (n = 3)	9 mo-6 yrs	Dengue hemorrhagic fever (2), Liver failure & DIC (2), epistaxis (1), GI bleeding (1), hepatoblastoma (1)	LD = 40-180; : CI = 16.5-33.5 mcg/kg/hr	Bleeding cessation and reduction of PT in all patients
Blatt[29]	Case Report (n = 3)	8-19 yrs	Pulmonary hemorrhage (1), hemorrhagic cystitis(3), GI bleeding (2), in patient undergoing BMT	90-270	Bleeding decreased in 2 of 3 patients with subsequent development of new bleeding in both
Morenski[22]	Case Series (n = 3)	5 wks-11 yrs	Coagulopathy secondary to cerebral injury	90	Correction of PT and INR in all patients
Park[38]	Case Report (n = 3)	5 mo-17 yrs	Coagulopathy requiring urgent neurosurgery	40-90	Correction of PT and INR after one rFVIIa dose in all patients; One patient (5 mos.) required additional dose intraoperatively for excessive bleeding
Chino[39]	Case Report (n = 2)	6 yrs 7 yrs	Liver injury related hemorrhage	90	Cessation of bleeding and correction of coagulopathy in both patients
Hartmann[40]	Case Report (n = 2)	9 yrs 14 yrs	Neurosurgical related hemorrhage	100-120	Hemostasis achieved in both patients, with the 9 year-old requiring 2 doses
Tobias[31]	Case Report (n = 1)	11 mo	Hepatic dysfunction, bleeding from esophageal varices and coagulopathy	90	Correction of coagulopathy and no additional active bleeding
Tobias[41]	Case Report (n = 1)	4 mo	Coagulopathy post cardiac surgery	70	Correction of PT and INR, and diminished sanguinous chest tube output
Leibovitch[42]	Case Report (n = 1)	10 wks	Pulmonary hemorrhage after cardiac surgery	100	Bleeding cessation after four doses

BMT, bone marrow transplant; CI, continuous infusion; CPB, cardiopulmonary bypass; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LD, loading dose; NR, not reported; PT, prothrombin time; rFVIIa, recombinant factor VIIa;
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REFERENCES

1. NovoSeven [package insert]. Bagsvaerd, Denmark; Novo Nordisk A/S; 2006.
2. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood 2004;104:3858-3864.
3. Franchini M, Zaffanello M, Veneri D. Recombinant factor VIIa. An update on its clinical use. Thromb Haemost 2005;93:1027-1035.
4. Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 2005;33:883-890.
5. Hoffman M, Monroe DM. A cell-based model of hemostasis. Thromb Haemost 2001;85:958-965.
6. 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;114:114-120.
7. Monroe DM, Hoffman M, Allen GA, et al. The factor VII-platelet interplay: effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopathia. Semin Thromb Hemost 2000;26:373-377.
8. Rapaport SI, Rao LV. Initiation and regulation of tissue factor-dependent blood coagulation. Arterioscler Thromb 1992;12:1111-1121.
9. Rapaport SI, Rao LV. The tissue factor pathway: how it has become a "prima ballerina". Thromb Haemost 1995;74:7-17.
10. Monroe DM, Hoffman M, Oliver JA, et al. Platelet activity of high-dose factor VIIa is independent of tissue factor. Br J Haematol 1997;99:542-547.
11. Mathew P. The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics. A systematic review. Thromb Haemost 2004;92:738-746.
12. Ekert H, Brizard C, Eyers R, et al. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. Blood Coagul Fibrinolysis 2006;17:389-395.
13. Tobias JD, Groeper K, Berkenbosch JW. Preliminary experience with the use of recombinant factor VIIa to treat coagulation disturbances in pediatric patients. South Med J 2003;96:12-6.
14. Pychynska-Pokorska M, Moll JJ, Krajewski W, et al. The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. Pediatr Crit Care Med 2004;5:246-250.
15. Razon Y, Erez E, Vidne B, et al. Recombinant factor VIIa (NovoSeven) as a hemostatic agent after surgery for congenital heart disease. Paediatr Anaesth 2005;15:235-240.
16. Pettersson M, Fischler B, Petrini P, et al. Recombinant FVIIa in children with liver disease. Thromb Res 2005;116:185-197.
17. Brown JB, Emerick KM, Brown DL, et al. Recombinant factor VIIa improves coagulopathy caused by liver failure. J Pediatr Gastroenterol Nutr 2003;37:268-272.
18. Kalicinski P, Markiewicz M, Kaminski A, et al. Single pretransplant bolus of recombinant activated factor VII ameliorates influence of risk factors for blood loss during orthotopic liver transplantation. Pediatr Transplant 2005;9:299-304.
19. 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;121:477-481.
20. Poon MC, D'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. J Thromb Haemost 2004;2:1096-1103.

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21. Heisel M, Nagib M, Madsen L, et al. Use of recombinant factor VIIa (rFVIIa) to control intraoperative bleeding in pediatric brain tumor patients. Pediatr Blood Cancer 2004;43:703-705.
22. Morenski JD, Tobias JD, Jimenez DF. Recombinant activated factor VII for cerebral injury-induced coagulopathy in pediatric patients. Report of three cases and review of the literature. J Neurosurg 2003;98:611-616.
23. Chuansumrit A, Chantarojanasiri T, 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 1):S101-105.
24. Wittenstein B, Ng C, Ravn H, et al. Recombinant factor VII for severe bleeding during extracorporeal membrane oxygenation following open heart surgery. Pediatr Crit Care Med 2005;6:473-476.
25. Egan JR, Lammi A, Schell DN, et al. Recombinant activated factor VII in paediatric cardiac surgery. Intensive Care Med 2004;30:682-685.
26. Mariani G, Testa MG, Di Paolantonio T, et al. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. Vox Sang 1999;77:131-136.
27. Tobias JD, Simsic JM, Weinstein S, et al. Recombinant factor VIIa to control excessive bleeding following surgery for congenital heart disease in pediatric patients. J Intensive Care Med 2004;19:270-273.
28. Atkison PR, Jardine L, Williams S, et al. Use of recombinant factor VIIa in pediatric patients with liver failure and severe coagulopathy. Transplant Proc 2005;37:1091-1093.
29. Blatt J, Gold SH, Wiley JM, et al. Off-label use of recombinant factor VIIa in patients following bone marrow transplantation. Bone Marrow Transplant 2001;28:405-407.
30. Kalicinski 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;31:378-379.
31. Tobias JD, Berkenbosch JW. Synthetic factor VIIa concentrate to treat coagulopathy and gastrointestinal bleeding in an infant with end-stage liver disease. Clin Pediatr (Phila) 2002;41:613-616.
32. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. Haemophilia 2004;10:352-359.
33. Santagostino E, Morfini M, Rocino A, et al. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. Thromb Haemost 2001;86:954-958.
34. O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295:293-298.
35. Levy JH, Fingerhut A, Brott T, et al. Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile. Transfusion 2006;46:919-933.
36. 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;85:748-749.
37. Mathew P, Winter SS, Frost JD, et al. Novel applications of recombinant factor VIIa for the management of pediatric coagulopathic diseases. J Pediatr Hematol Oncol 2003;25:499-502.
38. Park P, Fewel ME, Garton HJ, et al. Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. Neurosurgery 2003;53:34-38; discussion 8-9.
39. Chino J, Paolini D, Tran A, et al. Recombinant activated factor VII as an adjunct to packing for liver injury with hepatic venous disruption. Am Surg 2005;71:595-597.

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40. Hartmann M, Sucker C, Messing M. Recombinant activated factor VII in the treatment of near-fatal bleeding during pediatric brain tumor surgery. Report of two cases and review of the literature. J Neurosurg 2006;104:55-58.
41. 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.
42. Leibovitch L, Kenet G, Mazor K, et al. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. Pediatr Crit Care Med 2003;4:444-446.

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