

Applicability and safety of recombinant activated factor VII to control non-haemophilic haemorrhage: investigational experience in 265 children

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Summary. Experience of recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) to control haemorrhage in non-haemophilic children is limited. The object of this study was to examine the applicability and safety of rFVIIa amongst a group of non-haemophilic paediatric subjects. Details of all non-haemophilic children ≤ 16 years receiving rFVIIa whose data were recorded in the investigational, internet-based registry, *haemostasis.com* were analysed. A total of 265 children (mean age 7.7 years) were treated with rFVIIa; the median dose administered was $78.4 \mu\text{g kg}^{-1}$ body weight (range 9.0–393.4) and the median total dose received $100.0 \mu\text{g kg}^{-1}$ body weight (range 10.9–1341.2). Therapeutic areas included surgery (34.5%), coagulopathy (including thrombocytopenia; 29.0%), spontaneous bleeding

(17.2%), trauma (8.4%) and intracranial haemorrhage (4.5%). Two patients experienced thromboembolic events following administration of rFVIIa. Thirty-nine patients died on account of haemorrhage or complications relating to their underlying condition; neither the thromboembolic events nor the deaths were related to rFVIIa administration. Bleeding stopped in 118/237 (49.8%), markedly decreased in 54/237 (22.8%), decreased in 51/237 (21.5%), remained unchanged in 13/237 (5.5%) and increased in 1/237 (0.4%) patients. These results suggest that rFVIIa is safe and widely applicable in children to control non-haemophilic haemorrhage.

Keywords: children, haemorrhage, haemostasis, paediatric, rFVIIa, safety

Introduction

Recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) was originally developed for the treatment of bleeding episodes in patients with haemophilia A or haemophilia B with inhibitors towards FVIII or FIX, respectively. It is believed to exert its effects via a local procoagulant mechanism involving binding to the tissue factor at sites of vascular damage [1,2]. At pharmacological doses, rFVIIa binds to the surfaces of activated platelets and initiates a throm-

bin burst, independent of the tissue factor (FVIII or FIX), which leads to the formation of a stable clot; it may also increase clot stability via enhancement of thrombin-activatable fibrinolysis-inhibitor-dependent downregulation of fibrinolysis [3,4].

Increasingly, rFVIIa is being used as a potent local procoagulant for the treatment of acute haemorrhage in other situations [5–8]. These include trauma, surgery, cardiac surgery and obstetrics. In February 2004, rFVIIa was approved by the European Medicines Evaluation Agency for the treatment of haemorrhage associated with congenital FVII deficiency or platelet-refractory Glanzmann's thrombasthenia, highlighting its potential in the management of haemorrhage in patients with congenital bleeding disorders. However, in terms of its use in children, investigational data on rFVIIa are relatively scarce and generally involve small numbers of patients, which is largely on account of the ethical and practical difficulties of performing clinical trials in

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this population [5–8]. They include the use of rFVIIa during spinal fusion surgery [9] and neurosurgery [10]; for the management of bleeding events associated with different types of coagulopathy [11–17] and for the treatment of postoperative cardiac surgical bleeding [18–21]. Other single case reports and small case aggregates encompass a variety of therapy areas.

In situations in which clinical trials are difficult to perform, such as in children, voluntary registry submissions have provided useful preliminary insight into the investigational use of drugs. Accordingly, an international, internet-based registry, *haemostasis.com*, was established to capture clinical experiences relating to the investigational use of rFVIIa in the management of severe haemorrhages. Whilst establishment and running of the registry were supported by a grant from Novo Nordisk, its administration, and the collection and handling of data, have been independently managed and overseen by a steering committee of independent physicians. Between its launch in June 2001 and closure for data analysis in December 2003, more than 1100 entries covering a range of indications have been recorded. We present here the data from *haemostasis.com* relating to the use of rFVIIa in patients ≤ 16 years of age. The areas covered include therapeutic indications, patient characteristics, dosing strategies, safety and data relating to possible efficacy.

Materials and methods

All cases outlining the use of rFVIIa in patients ≤ 16 years of age were identified from searches of the *haemostasis.com* registry. To minimize potential bias, all cases were included without preselection, regardless of whether or not data were available for all data categories. For each category, the number of cases with available data is provided.

Inclusion criteria

Informed consent from patients (and/or parents/guardians/caregivers) was obtained before case data were recorded on *haemostasis.com*. In the current analysis, criteria for inclusion were: age ≤ 16 years and consent from case providers for their data to be included in the analysis.

Data analysis

The registry template requested the following information from each case provider: patient's age,

gender, weight and underlying condition; bleeding severity; type of surgery; all medications administered before and after the use of rFVIIa, including antifibrinolytic therapy and haematological replacement therapy [number of units of blood products, e.g. packed cells, whole blood, fresh frozen plasma (FFP), cryoprecipitate, platelets; volume of crystalloids/colloids]; dose of rFVIIa administered ($\mu\text{g kg}^{-1}$ body weight), and total dose received ($\mu\text{g kg}^{-1}$ body weight), number of doses and interval between doses; response of bleeding to rFVIIa (classified as 'stopped', 'markedly decreased', 'decreased', 'unchanged' or 'increased') and time to response; any adverse events (AEs) or deaths and whether these were related to rFVIIa (classified as 'probably or possibly related', 'unlikely to be related' or 'not related'); the results of any laboratory tests conducted, including coagulation parameters, such as the international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT) and activated PTT (APTT); the patient's outcome; and a case description. Massive haemorrhage was defined as requiring ≥ 19 units of any blood products (i.e. packed cells, whole blood, FFP and/or platelets). Less severe grades of haemorrhage were determined subjectively on clinical grounds.

Statistical analysis

Descriptive statistics [mean (\pm standard deviation), median, range] were calculated for numerical data and frequency distributions for categorical data. Linear regression analysis was used to investigate the possibility of a relationship between patient age and the dose of rFVIIa administered. Statistical comparisons of values (INR, PT, PTT, APTT, and use of blood products and crystalloids/colloids) before and after rFVIIa administration were made using the non-parametric Wilcoxon paired-sample test; cases were included in the comparison only when data were available for both 'before rFVIIa' and 'after rFVIIa'. The non-parametric Mann–Whitney test was used to compare the dose of rFVIIa that was administered to patients who suffered a massive haemorrhage with those who did not suffer a massive haemorrhage, and also to compare the ages and weights of these groups of patients.

Results

More than 1100 cases were entered onto the *haemostasis.com* website between June 2001 and December 2003. Of these, 265 cases described the use of rFVIIa in non-haemophilic patients ≤ 16 years

of age. All 265 cases were included in the present analysis.

Patient characteristics

Patients had a mean age of 7.7 (± 5.8) years (median 7; range 0–16; $n = 265$) and a mean weight of 27.9 (± 19.8) kg (median 22; range 1.4–80; $n = 258$). There were 151 males (57.0%) and 112 females (42.2%); gender was unspecified in two cases (0.8%). Table 1 provides a breakdown of the therapeutic areas in which rFVIIa was used.

Dosing strategies

The median dose, number of doses and the median total dose per kg of rFVIIa received are shown in Table 2. Linear regression analysis revealed no clear correlation between patient's age and the dose of rFVIIa administered (data not shown). Data concerning the number of doses administered were available in 258/265 cases. Of these, 139 patients (53.7%) received a single dose of rFVIIa; 68 patients (26.4%) received two doses; 28 patients (10.9%) received three doses; 12 patients (4.7%) received four doses; and 11 (4.3%) patients received ≥ 5 doses. Details of all patients who received ≥ 5 doses are outlined in Table 3; the majority of these patients

had bleeding events associated with non-haemophilic coagulopathies.

Twenty-eight patients (10.6%) suffered massive haemorrhage during the 24 h preceding rFVIIa administration. The median total dose of rFVIIa administered to patients in this subgroup was $110.8 \mu\text{g kg}^{-1}$ [mean $186.1 \mu\text{g kg}^{-1}$ (± 242.4); range 26.7–1229.3], compared with a median total dose of $100.0 \mu\text{g kg}^{-1}$ [mean $162.2 \mu\text{g kg}^{-1}$ (± 180.2); range 10.9–1341.2] that was administered to patients who did not suffer a massive haemorrhage ($P = ns$). Patients who suffered a massive haemorrhage weighed significantly more than those who did not [mean weights: 37.9 (± 25.7) kg vs. 26.8 (± 18.8) kg; $P < 0.05$], and tended to be older [mean ages: 9.6 (± 6.2) vs. 7.5 (± 5.7) years; $P = 0.065$]. For both groups, the median number of doses that was administered was 1 [mean 2.3 (± 4.0); range 1–21 for patients who suffered a massive haemorrhage; mean 2.0 (± 2.3); range 1–23; $P = ns$ for those without a massive haemorrhage].

Adverse events

Two patients (0.8%) experienced thromboembolic events following administration of rFVIIa. In each case, the physician involved considered the thrombotic event unlikely to be related to rFVIIa administration:

Patient 1 A 15-year-old girl with end-stage renal failure on haemodialysis underwent cadaveric renal transplantation. There was normal surgical haemostasis during the initial phases of surgery, however following vascular anastomosis of the donor kidney, and during surgical closure, excessive bleeding was noted from multiple sites. Clinically, the bleeding was consistent with a systemic coagulopathy, but this was not confirmed by laboratory studies. The patient became hypotensive and dropped her haemoglobin to 28g L^{-1} . She required massive transfusional support. Despite administration of desmopressin, fresh frozen plasma, cryoprecipitate and platelets, bleeding continued. An exploratory laparotomy failed to demonstrate a focal bleeding point. Administration of rFVIIa ($135 \mu\text{g kg}^{-1}$) produced an immediate reduction in generalized bleeding and improvement in coagulation parameters. The patient was given packed cells to correct her anaemia but did not require additional blood products. Subsequently, renal impairment developed on account of biopsy-proven acute tubular necrosis. There was no evidence of renal vascular thrombosis on Doppler studies. One month following transplantation, the patient

Table 1. Therapeutic areas in which recombinant activated factor VII was used in paediatric registry patients.

Therapeutic area	<i>n</i>	%
Surgery (perioperative)	152	34.5
Coagulopathy, including thrombocytopenia	128	29.0
Spontaneous bleeding	76	17.2
Trauma	37	8.4
Intracranial haemorrhage	20	4.5
Sepsis	17	3.9
Obstetrical and gynaecological bleeding	11	2.5
Total*	441	100

*Individual cases could be categorized under more than one therapeutic area.

Table 2. Summary of recombinant activated factor VII dosing strategies in paediatric registry patients.

Parameter	<i>N</i>	Mean	SD	Median	Range
Dose ($\mu\text{g kg}^{-1}$)	520*	79.6	43.8	78.4	9.0–393.4
Number of doses (<i>n</i>)	258	2.1	2.5	1.0	1–23
Total dose administered ($\mu\text{g kg}^{-1}$)	253	164.5	186.7	100.0	10.9–1341.2

*520 doses administered to a total of 255 patients.

Table 3. Details of patients receiving multiple (≥ 5) doses of recombinant activated factor VII ($n = 11$).

Case	Dose ($\mu\text{g kg}^{-1}$) (Number of doses)	Cumulative dose ($\mu\text{g kg}^{-1}$)	Weight (kg)	Total dose (mg)	Therapeutic area(s)
1	200 (2), 75 (3)	625	2	0.65	Coagulopathy (1-day old with immature liver)
2	200 (6)	1200	6	7.2	Coagulopathy (Kasabach–Merritt syndrome), ICH, surgery
3	90 (6)	540	40	21.6	Coagulopathy (von Willebrand's disease); surgery
4	NP (7)	NP	NP	50.4	Coagulopathy (FXI deficiency + inhibitors); surgery
5	113 (8)	904	2.7	2.4	Coagulopathy (preterm newborn with dilutional coagulopathy and DIC); trauma
6	100 (4), 60.1 (4)	640.4	15	9.6	Coagulopathy (FX deficiency); spontaneous bleeding
7	55 (2), 110 (7)	880	43.6	38.4	Coagulopathy (FV + FVII deficiency); surgery
8	110 (10)	1100	3	3.3	Coagulopathy (septic shock); sepsis; spontaneous bleeding
9	71 (19)	1349	34	45.9	Trauma [†]
10	58 (21)	1218	41	50	Surgery [‡]
11	24 (1), 12 (22)	288	50	14.4	Coagulopathy (FVII deficiency); surgery (rFVIIa used prophylactically for major orthopaedic spinal surgery)

DIC, disseminated intravascular coagulation; FV, factor V; FVII, factor VII; FX, factor X, FXI, factor XI, ICH, intracranial haemorrhage; rFVIIa, recombinant activated factor VII; NP, not provided.

[†]A 9-year-old boy with repeated bleeding into the right knee and upper right leg, which could not be controlled with bed-rest and treatment with fresh frozen plasma (FFP). Patient had no apparent coagulopathy. Admitted after fall on same knee, causing serious bleeding; movement of the knee was not possible and FFP did not stop the bleeding; rFVIIa treatment was commenced at 4-h intervals. The swelling of the knee and upper right leg rapidly decreased and the patient could be mobilized within a few days. Re-bleeding was not observed.

[‡]An 11-year-old boy who had a kidney transplantation as a result of focal segmental glomerulosclerosis. Postoperative bleeding was initially treated with packed cells, FFP and platelet concentrates without success. rFVIIa was administered once and the bleeding stopped. Re-bleeding occurred after 2 days and rFVIIa treatment was repeated and continued for several days at increasing intervals. No further re-bleeding was observed.

developed a subclavian deep venous thrombosis at the site of a central venous catheter. The line was removed and the patient anticoagulated. She was discharged from hospital.

Patient 2 A 16-year-old female with end-stage renal failure secondary to juvenile nephronophthisis (medullary cystic disease) had previously undergone a cadaveric renal transplant at age 2; this had lasted 10 years before she required further haemodialysis. Her extensive past medical history included hypertension, renal osteodystrophy, small-vessel ischaemic heart disease, mitral stenosis, inferior vena cava (IVC) thrombosis and a deep venous thrombosis (DVT) with negative thrombophilia screen. The patient was wheelchair-bound and in a poor physical condition. She underwent a second cadaveric renal transplant under immunosuppressive cover (tacrolimus, prednisolone). Following surgery, Doppler ultrasound showed both renal vessels to be functioning normally. On day 2, the patient became hypotensive and required administration of inotropes. An exploratory laparotomy demonstrated a small bowel perforation. Over the next 24 h, she experienced significant blood loss with evidence of hypotension, disseminated intravascular coagulation (DIC), dilutional coagulopathy, lactic acidosis and abdominal tamponade. The patient received multiple transfusions of packed cells, as well as administration of FFP, cryoprecipitate,

platelets, vitamin K, protamine, desmopressin and aprotinin. Subsequently, rFVIIa was given on day 3 at a dose of $90 \mu\text{g kg}^{-1}$. This resulted in improved haemostasis and coagulation parameters. By day 6, there was no evidence of renal function and the patient required dialysis. A third laparotomy was performed to repair a jejunal loop. The patient's condition worsened over subsequent days; she required maximal inotropes and there was evidence of a non-viable kidney on ultrasound. A fourth laparotomy revealed gangrenous sigmoid and descending colon. The transplanted kidney was removed. It was decided to institute palliative therapy and the patient died on the 10th day after transplantation. Re-bleeding was reported as an AE in five patients (1.9%). In each case, the physician involved considered the episode unlikely to be related to rFVIIa administration.

Mortality

A total of 39/265 patients (14.7%) died. Causes of death were as follows: non-ischaemic brain injury ($n = 6$); cardiorespiratory failure ($n = 5$); uncontrolled haemorrhage ($n = 4$); respiratory distress syndrome ($n = 1$); multiple organ failure ($n = 11$); renal failure, acute ($n = 1$); liver failure ($n = 3$); polytrauma ($n = 2$); septic shock ($n = 1$); not provided ($n = 5$). Any potential connection between cause of death and rFVIIa administration was

provided in 34/39 cases; in none of these cases was the patient's death considered by their treating physician to have been related to rFVIIa administration. Mortality data by therapeutic area are shown in Table 4. Mortality rates were highest in patients with bleeding related to sepsis (23.5%) and trauma (21.6%).

Blood loss and response to rFVIIa

Although estimates of blood loss are known to be inaccurate, a numerical assessment of bleeding rates before and after the administration of rFVIIa would have been desirable. However, this was not feasible for cases entered into the *haemostasis.com* registry, as the situations in which rFVIIa was administered varied greatly, not only in terms of therapeutic area (e.g. trauma, perioperative haemorrhage, spontaneous haemorrhage), but also in terms of the timing of administration. In the absence of a quantitative assessment, case providers were requested to make a qualitative judgement of the effect of rFVIIa administration on blood loss, by categorizing the overall effect of rFVIIa on haemorrhage. This information was available for 237/265 cases: bleeding

was recorded as having 'stopped' in 118 patients (49.8%), being 'markedly decreased' in 54 patients (22.8%), 'decreased' in 51 patients (21.5%), 'unchanged' in 13 patients (5.5%) and 'increased' in one patient (0.4%). Bleeding response to rFVIIa according to therapeutic area is shown in Table 5.

Bleeding outcomes following rFVIIa administration were recorded in 22/28 patients who suffered massive haemorrhage, and in 215/237 patients who did not suffer a massive haemorrhage. In patients who suffered a massive haemorrhage, bleeding stopped in five patients (22.7%), markedly decreased in 10 patients (45.5%), decreased in six patients (27.3%) and did not change in one patient (4.5%). In patients who did not suffer a massive haemorrhage, bleeding stopped in 113 patients (52.5%), markedly decreased in 44 patients (20.5%), decreased in 45 patients (20.9%), did not change in 12 patients (5.6%) and increased in one patient (0.5%).

Requirement for blood products and crystalloids/colloids

During the 24 h before and after administration of rFVIIa, 158 and 114 patients required replacement blood products, respectively. The requirement for blood products significantly decreased after rFVIIa administration ($P < 0.001$; Fig. 1a). By comparison, similar numbers of patients required crystalloids/colloids during the 24 h before and after rFVIIa administration (Fig. 1b).

Coagulation parameters

A number of cases had missing results for coagulation parameters and there was variability in the specific parameters used. Available data demonstrated that INR, PT, PTT and APTT all improved following administration of rFVIIa (Fig. 2).

Table 4. Mortality by therapeutic area.

Therapeutic area	Total number of patients* (n)	Mortality (%)	
		Yes	No
Surgery	152	15.1	84.9
Coagulopathy	128	10.2	89.8
Spontaneous bleeding	76	11.8	88.2
Trauma	37	21.6	78.4
Intracranial haemorrhage	20	15.0	85.0
Sepsis	17	23.5	76.5
Obstetrics and gynaecology	11	0	100.0

*Mortality data were available for all patients.

Table 5. Bleeding response to recombinant activated factor VII by therapeutic area.

Therapeutic area	Total number of patients (n)	Number of patients with data for bleeding response (n)	Bleeding response to rFVIIa (%)				
			Stopped	Markedly decreased	Decreased	Not changed	Increased
Surgery	152	138	51.5	18.8	26.8	2.9	0
Coagulopathy	128	112	49.1	28.6	15.2	6.2	0.9
Spontaneous bleeding	76	66	54.6	28.8	12.1	3.0	1.5
Trauma	37	34	35.3	32.4	17.6	14.7	0
Intracranial haemorrhage	20	18	61.1	16.7	16.7	5.5	0
Sepsis	17	13	46.1	23.1	30.8	0	0
Obstetrics and gynaecology	11	9	11.1	33.3	44.5	11.1	0

rFVIIa, recombinant activated factor VII.

Note: individual cases could be categorized under more than one therapeutic area.

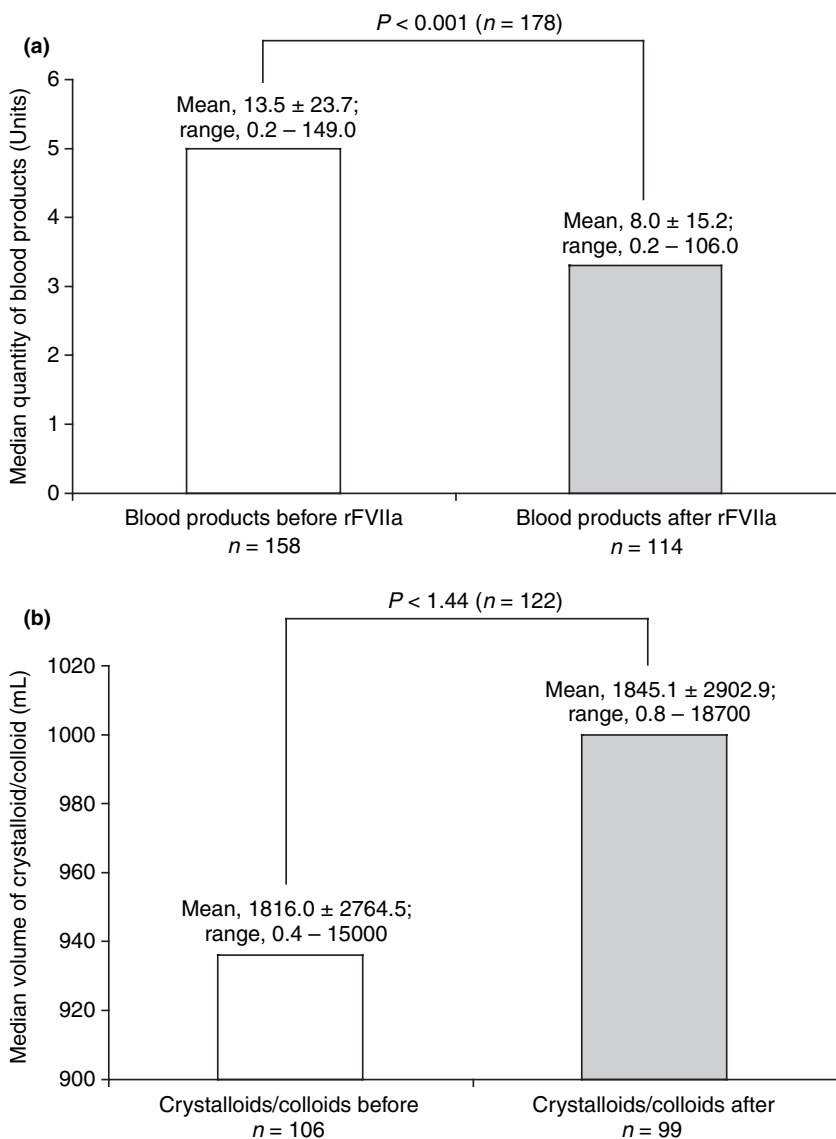


Fig. 1. Median quantities of blood products (a) and crystalloids/colloids (b) given to haemorrhaging paediatric registry patients in the 24 h before and after administration of recombinant activated factor VII (rFVIIa).

Discussion

We have reviewed 265 cases of investigational use of rFVIIa for the management of severe haemorrhage in patients who did not have haemophilia and were aged ≤ 16 years. These children were all seriously ill and at high risk of complications arising from ongoing haemorrhage and a wide range of underlying disease processes. Our findings indicate that rFVIIa provides a favourable safety profile and may have benefits in reducing bleeding in this population.

Although the mechanism of action of rFVIIa has not been fully elucidated [22,23], use of rFVIIa is associated with a theoretical risk of thromboembolic events on account of its effects on thrombin generation. In the cohort of patients from this registry,

only 2/265 (0.8%) children suffered thromboembolic events after receiving rFVIIa and, in both cases, the physician involved did not consider the event to be rFVIIa related. Moreover, of the 39/265 (14.7%) patients that died, review of the causes of death and the assessment of the physicians involved (where available) did not suggest any likely relationship between the administration of rFVIIa and adverse outcomes. We believe this supports a favourable safety profile for the use of rFVIIa and demonstrates its low potential to cause thromboembolic complications in children.

These findings are supported by previous clinical experience with rFVIIa: the licensed use of more than 700 000 doses of rFVIIa between 1996 and April 2003 (for patients with haemophilia A and

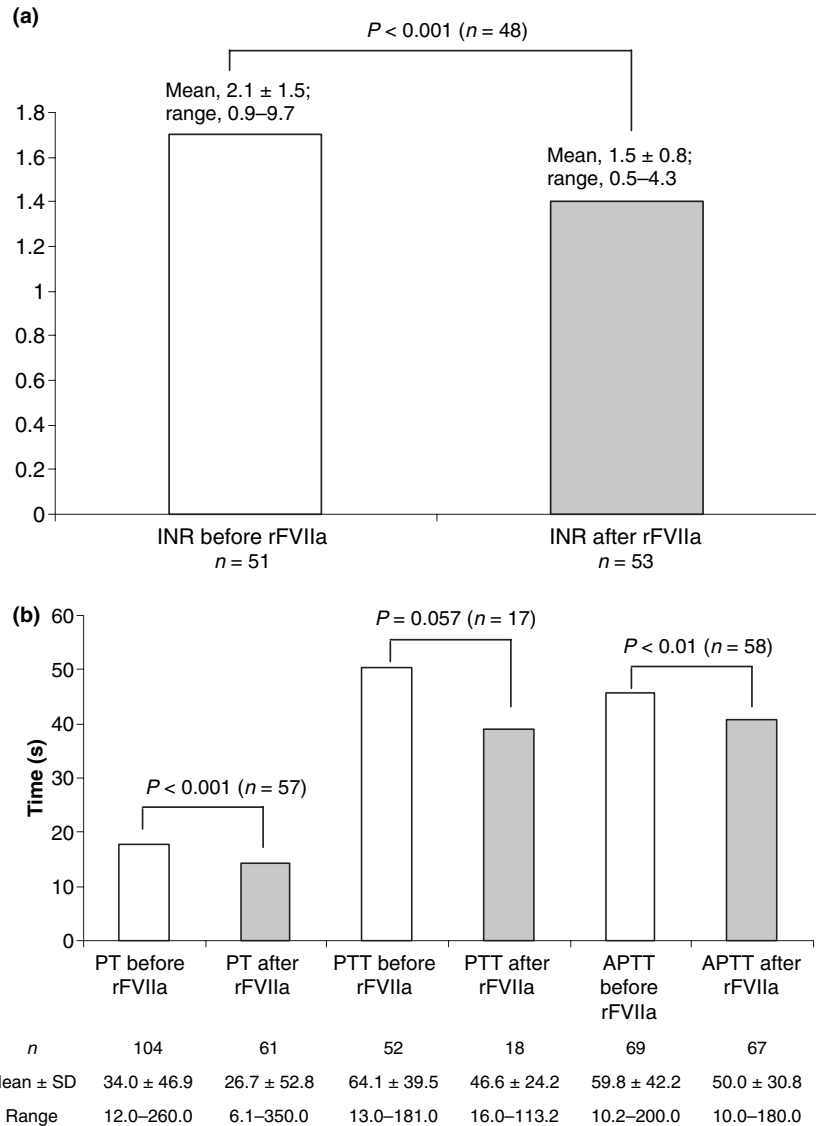


Fig. 2. Median values for international normalized ratio (INR) (a), and prothrombin time (PT), partial thromboplastin time (PTT) and activated PTT (APTT) (b) in the 24 h before and after administration of recombinant activated factor VII (rFVIIa) to paediatric registry patients.

haemophilia B) resulted in only 16 thromboembolic events and two cases of DIC, indicating the risks to be low [24]. Furthermore, in numerous case reports of the off-label use of rFVIIa for the management of severe haemorrhage in adults, there seems to be a rare occurrence of thromboembolic complications, which is consistent with our findings in this large paediatric cohort. In comparison, O'Connell *et al.* recently reviewed 168 reports that were submitted to the Federal Drug Administration concerning thromboembolic events, of which 151 occurred in off-label indications, including adults and children[25]. The authors found that although such events were relatively uncommon, they often resulted in serious morbidity and mortality. Unfortunately, analysis of the relationship between AEs and rFVIIa was hindered by concomitant medications,

pre-existing medical conditions, confounding by indication and inherent limitations of passive surveillance. They concluded that randomized controlled trials are needed to establish the safety and efficacy of rFVIIa in patients without haemophilia.

Importantly, although the incidence of venous thrombosis in children is rare, these events represent significant clinical entities and have gained increasing recognition in the past decade. Indeed, efforts to track post-thrombotic outcomes have shown that the long-term complications, including mortality, recurrence and post-thrombotic syndrome, are considerable. Moreover, the increased survival of patients as a result of therapeutic advances and improved clinical expertise means that the incidence of thromboembolic complications is likely to become even more significant. Multiple clinical underlying

conditions, as well as congenital prothrombotic disorders, are thought to contribute to the development of venous thrombosis and their outcome is often difficult to predict [26]. A recent Canadian survey identified those patient factors and thrombus characteristics that have been used by physicians to label a venous thromboembolism as clinically important in children [27]. Such methods may assist in identifying patients for treatment, thereby reducing the long-term morbidity and mortality that is associated with this condition.

It is difficult to draw any firm conclusions concerning the potential efficacy of rFVIIa in treating uncontrollable haemorrhage in this population. Although the data gathered from the registry are uncontrolled and qualitative, there is an apparent trend towards severe haemorrhage stopping or markedly decreasing following the administration of rFVIIa. However, it is likely that the patient will have received multiple therapeutic interventions around this time and it is not possible to relate clinical efficacy to a particular intervention without conducting the necessary randomized controlled trials. The apparent reductions in the requirements for red blood cells and coagulation products, although potentially indicative of benefit, are subject to the same caveats. At present, there is no laboratory test for monitoring the effect of rFVIIa, and the coagulation tests conducted cannot be used to make any conclusions regarding the efficacy of rFVIIa.

Although there is evidence demonstrating that the rate of clearance of rFVIIa is faster [28], and the half-life is shorter [29], in paediatric than in adult patients, we found neither evidence of physicians using higher or more frequent dosing regimens than those used in adults, nor of the requirement for such: the median dose of rFVIIa administered was nearly $80 \mu\text{g kg}^{-1}$ body weight, similar to the $90 \mu\text{g kg}^{-1}$ body weight dose that is recommended for the treatment of patients with haemophilia A or B and Glanzmann's thrombasthaenia [24], and >50% of patients received only a single dose of rFVIIa. Our findings also showed that dosing of rFVIIa was higher in patients who suffered massive haemorrhage compared with those that did not and, in general, these patients with massive haemorrhage were heavier on account of their older age. However, it is difficult to interpret these data in the absence of detailed information on the standardization of massive haemorrhage with respect to the patient's weight.

A recent publication by the Israeli Multidisciplinary rFVIIa Task Force has set out guidelines for the off-label use of rFVIIa in patients with uncontrolled

bleeding, with a particular emphasis on trauma patients [30]. These guidelines are based on extensive literature searches and experience gained from a prospective national registry of multi-trauma patients treated with rFVIIa. They recommend that rFVIIa be administered as adjunctive therapy to concomitant surgical measures at an initial starting dose of approximately $120 \mu\text{g kg}^{-1}$ for massive haemorrhage, administered over 2–5 min; if haemorrhage persists beyond 15–20 min, an additional dose of approximately $100 \mu\text{g kg}^{-1}$ should be considered [30]. The proportion of trauma patients whose bleeding stopped following rFVIIa administration was lower in the present study (35.3%) than in the Israeli Multidisciplinary rFVIIa Task Force study (72%). One explanation for these differences is that the majority of patients in the present study were administered rFVIIa as a last resort, and it is possible that the bleeding cessation rate for trauma patients may have been higher if rFVIIa had been administered earlier, or at a higher dose, as recommended by the Task Force guidelines; however, this is purely speculative, and further studies are required before any efficacy recommendations for paediatric patients can be made [30].

The current study has several important limitations. First, as the data were derived from a voluntary registry, they were completely uncontrolled – physicians could decide whether or not to submit cases to the registry, and we cannot discount the possibility of a bias towards the reporting of data on successful rather than unsuccessful cases. Second, datasets for individual cases were often incomplete, and as we did not wish to introduce any further potential bias by excluding cases on the basis of missing data, all cases were included, regardless of data completeness. Third, in designing a registry for physicians from a wide range of countries, disciplines and institutions, ease of data entry was important. Consequently, much of the data are qualitative and subjective, precluding robust statistical analysis across the range of therapeutic areas reported. Nevertheless, we believe that the registry provides valuable information on the investigational use of rFVIIa in a large number and range of 'real-world' clinical settings.

In conclusion, we have reported the use of rFVIIa for severe haemorrhage in 265 children with a wide variety of underlying conditions but without haemophilia and in a wide range of therapeutic areas. Although the data are not controlled, this is a large patient cohort. It is not possible to make definitive statements regarding potential efficacy, although some qualitative data may be encouraging. However,

it is positive and important that only two thromboembolic events occurred in these children following rFVIIa administration, neither of which seemed to be related to therapy. This provides some confidence in the safety profile of this novel haemostatic therapy and should encourage physicians to undertake the necessary randomized, controlled trials to further investigate its potential safety and efficacy.

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Disclosures

Dr. Herbertson has acted as paid consultant to Novonordisk Inc. and received honoraria for lectures as well as participating in a advisory board for Novonordisk. Dr. Kenet has acted as paid consultant to Novonordisk Inc. and received honorarium for lectures as well as participation in an advisory board for novonordisk pharmaceuticals.

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