INTRODUCTION

As described in detail in other chapters of this volume, conditions with excessive bleeding, as are seen with uterine rupture, placenta accreta, abruption and uterine atony, often require intensive resuscitation with blood components and coagulation factors. In such circumstances, blood transfusion may be life-saving, but on occasion involves exposing the patient to additional risks. Over the years, numerous efforts have been put forward to reduce these risks. One of the most spectacular is discussed in this chapter.

Recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) was developed for the treatment of spontaneous and/or surgical bleeding episodes in patients with hemophilia A or B with formation of allo-antibodies to FVIII or FIX after replacement therapy. rFVIIa is currently licensed for this indication in most countries worldwide. The US Food and Drug Administration (FDA) licensed rFVIIa on March 25, 1999 for bleeding episodes in patients with hemophilia A or B and inhibitors to FVIII or FIX. The FDA approved use of rFVIIa in 2005 for additional indications such as surgical procedures in patients with hemophilia A or B and inhibitors, and treatment of bleeding episodes in patients with factor VII deficiency. In Europe, it is also approved for use in bleeding episodes in patients with acquired hemophilia due to auto-antibodies against endogenous FVIII or FIX, surgical procedures in this group of patients, and Glanzmann’s thrombasthenia. Beyond its currently recognized indications, rFVIIa has been effectively used ‘off label’ on an empirical basis as a general hemostatic agent in a wide range of conditions characterized by impaired thrombin generation in non-hemophilic patients, many of whom are critically ill and refractory to other hemostatic treatment options.

Recently, rFVIIa was approved for the treatment of hemorrhage associated with congenital factor VII deficiency and Glanzmann’s thrombasthenia.

PECULIARITIES OF OBSTETRIC HEMORRHAGE

Patients who develop massive, life-threatening postpartum hemorrhage often have a combination of ‘coagulopathic’ diffuse bleeding in addition to ‘surgical bleeding’. Whereas bleeding from larger vessels may be controlled by surgeons using a variety of operations (see Chapters 49–53), the ability to control diffuse bleeding is limited and, in many cases, not feasible. Thus administration of hemostatic drugs that can control the coagulopathic component of blood loss may reduce mortality and morbidity in such patients. Clinical experience presently suggests that rFVIIa is a safe and effective hemostatic measure in severe obstetric hemorrhage, both as an adjunctive treatment to surgical hemostasis as well as a ‘salvage’ or ‘rescue’ therapy where postpartum hemorrhage is refractory to current pharmaceutical and ‘uterus sparing’ surgical techniques. The ‘evidence’ behind the preceding statement comes from three sources:

(1) Studies on its mechanism of action;
(2) Accumulating reports in the literature; and
(3) Data from clinical studies.

All suggest that rFVIIa has the potential to function as a ‘universal hemostatic agent’ across a range of indications characterized by impaired thrombin generation in non-hemophilic patients, many of whom are critically ill and refractory to other hemostatic treatment options.

The usual manner for treating postpartum hemorrhage includes, first, non-invasive/non-surgical methods, including administration of crystalloid solutions and/or red blood cells, uterine massage, uterotonic medications (oxytocin, ergotamine, prostaglandins), and, second, invasive/surgical methods, e.g. ligation of uterine vessels, ligation of iliac arteries, angiographic embolism of uterine/iliac arteries, or the B-Lynch procedure.
method. Unfortunately, the overall effectiveness of such procedures to arrest hemorrhage and prevent the need for emergency hysterectomy is estimated to be only about 50\%^{17,18}. Moreover, comparatively few centers worldwide have access to the physical equipment or surgical manpower resources necessary to conduct all the aforementioned procedures.

**COAGULATION FACTOR VII: THE HUMAN PROTEIN AND RECOMBINANT PRODUCT**

**Structure of the human FVII (hFVII)**

Human factor VII (eptacog alpha) is a serine protease (molecular weight 50 kDa) composed of 406 amino acid residues, belonging to the group of vitamin K-dependent coagulation glycoproteins. The primary site of FVII synthesis in humans is the liver. Factor VII is composed of four discrete domains: a \(\gamma\)-carboxyglutamic acid (Gla)-containing domain, two epidermal growth factor (EGF)-like domains, and a serine protease domain. All appear to be involved, to different extents, in an optimal interaction with tissue factor (TF). The Gla domain of factor VII is also essential for activation of factor X and other macromolecular substrates. The activation of factor VII to factor VIIa involves the hydrolysis of a single peptide bond between Arg152 and Ile153. The result is a two-chain molecule consisting of a light chain of 152 amino acid residues and a heavy chain of 254 amino acid residues held together by a single disulfide bond\(^{19,20}\) (Figures 1 and 2).

**Production of rFVIIa using recombinant DNA technique**

The development of rFVIIa was undertaken to alleviate the problems associated with the use of plasma-derived factor VIIa, such as limited supply and possible

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**Figure 1** Three-dimensional molecular structure of factor VII. Reproduced with permission from Novo Nordisk

**Figure 2** The active two-chain enzyme factor VIIa, is generated by specific cleavage AT Arg 152. Reproduced with permission from Novo Nordisk
viral contamination. Multiple steps were involved in the development of this recombinant protein. First, the human gene for factor VII, located on chromosome 13, comprising eight exons (coding regions), was isolated from the liver gene library. After standard amplification procedures used to generate multiple copies of the hFVII gene, it was transfected into a baby hamster kidney cell line. A master cell bank of the transfected cell line that secretes factor VII in a single-chain form into the culture medium was then established. During the last steps, proteolytic conversion by autocatalysis to the active two-chain form (rFVIIa) takes place in a chromatographic purification process, which was shown to remove exogenous viruses. No human serum or other proteins are used in the production of rFVIIa (see Chapter 72). The protein backbone is identical with human purified factor VIIa. The final product (rFVIIa), despite minor differences in carbohydrate composition, is structurally similar to plasma-derived factor VIIa.

**PHARMACOKINETIC STUDIES OF rFVIIa IN HUMANS**

The pharmacokinetics of single-bolus doses of rFVIIa have been studied in various adult populations: patients with hemophilia, patients with cirrhosis, and healthy volunteers. The pharmacokinetic parameter values of rFVIIa after bolus administration were similar. The elimination half-life ($t_{1/2}$) ranged from 2.45 to 2.72 h and clearance (CL) ranged from 32.8 to 34.9 ml/h/kg. Lindley and colleagues investigated the single-dose pharmacokinetics of rFVIIa, evaluated in three dose levels (17.5, 35.0, 70 µg/kg) in hemophilic A/B patients with inhibitors. The results of these investigations demonstrate that the mean $t_{1/2}$ of recombinant factor VIIa is independent of dose level.

Pharmacokinetic evaluations suggest the elimination of rFVIIa follows linear kinetics with a faster clearance rate and shorter $t_{1/2}$ when rFVIIa is administered for bleeding episodes (medians: 2.70 and 2.41 h, respectively) compared to non-bleeding indications (medians: 3.44 and 2.89 h, respectively). Therefore, the duration of action may be shorter when rFVIIa is used to control bleeding episodes. The average percentage of the preparation found in plasma was significantly lower after administration of rFVIIa in a dose of 70 µg/kg (42.7%) compared to doses of 17.5 µg/kg (50.1%) or 35 µg/kg (49.0%) ($p = 0.0067$). Additional doses for specific patient populations are warranted however. An increased elimination rate and lower recovery of rFVIIa during bleeding may be related to consumption through complex formation with TF exposed at the site of vessel damage and on the phospholipids exposed on the activated platelet surface. The volume of distribution at steady state ($V_d$), is two to three times that of plasma and similar to the half-life of recombinant factor VIIa.

**MECHANISM OF HEMOSTATIC ACTION OF rFVIIa**

Recombinant factor VIIa induces hemostasis at the site of injury. The mechanism of action includes the binding of factor VIIa to the exposed tissue factor-dependent pathway and, independently of tissue factor, activation of factor X directly on the surface of activated platelets localized to the site of injury. The formation of the TF/FVIIa or TF/rFVIIa complex at the site of injury is necessary to initiate hemostasis. TF is a membrane-bound glycoprotein, which normally is expressed on cells in the subendothelium and is only exposed following injury. Tissue injury disrupts the endothelial cell barrier that normally separates TF-bearing cells from the circulating blood. Once exposed to the blood, TF serves as a
POSTPARTUM HEMORRHAGE

high-affinity receptor for FVIIa. FVIIa is found in the circulation, comprising about 1% of the total circulating FVII protein mass in the plasma. It is endowed with very weak enzymatic activity, which only becomes fully realized upon binding to its cofactor, TF, at a site of vascular injury. Factor VIIa alone shows very little proteolytic activity, only attaining its full enzymatic potential when complexed to TF.

In studies using TF incorporated into lipid vesicles, van’t Veer and colleagues demonstrated that zymogen FVII acts as an inhibitor of FVIIa:TF-initiated thrombin generation. The addition of FVIIa at a concentration of 10 nmol/l in hemophilic conditions overcomes this inhibition and results in a thrombin generation equivalent to normal. These data suggest that the therapeutic effect of rFVIIa is due in part to its ability to overcome the inhibitory effect of physiologic FVII on FVIIa:TF-initiated thrombin generation.

However, if TF is no longer available or exposed to the clotting factors in the bloodstream, e.g. when a platelet plug covers the TF-containing subendothelial space, or when TF activity is inhibited by TFPI (tissue factor pathway inhibitor), then rFVIIa-mediated large-scale thrombin generation could take place on the activated platelet surface independently of TF.

The initial formation of a TF/FVIIa or TF/ rFVIIa complex allows activation of FIX and FX, and is crucial in generating the initial conversion of small amounts of prothrombin into thrombin (on the TF-bearing cells), which is essential to the amplification and propagation phase of coagulation. FXa cannot move to the platelet surface because of the presence of normal plasma inhibitors, but instead remains on the TF-bearing cell and activates a small amount of thrombin. Thrombin leads to the activation of platelets and FV and FVIII at the site of injury.

This small amount of thrombin is not sufficient for fibrinogen cleavage, but is critical for hemostasis, as it can activate platelets, activate and release FVIII from von Willebrand factor (vWF) or activate platelet and plasma FV, and FXI. FXa moves to the platelet surface, where it forms a complex with FVIIIa and activates FX on the platelet surface. The activated platelets provide for further thrombin generation. Platelet-surface FXa is relatively protected from normal plasma inhibitors and can complex with platelet-surface FVa, where it activates thrombin in quantities sufficient to provide for fibrinogen cleavage.

FXa, FVIIa and FVa bind efficiently to the surface of the activated platelet and further activation of FX into FXa occurs via the complex between FIXa and FVIIIa. During amplification, FXa complexes with FVa to generate thrombin and subsequently activate FV, FVIII and platelets.

At pharmacological concentrations (supraphysiological doses), rFVIIa also directly activates FX on the surface of locally activated platelets, helping to generate thrombin and fibrin (platelet-dependent TF-independent pathways). rFVIIa does not bind to resting platelets. Instead, the effect of high-dose rFVIIa (which only activates FX on activated platelets) is localized to the sites of vessel injury where TF is exposed and platelets are activated. This results in the conversion of prothrombin into large amounts of thrombin. The full thrombin burst mediated by FXa in complex with FVa is necessary for the formation of a fully stabilized and solid fibrin hemostatic plug.

rFVIIa works by producing a stable fibrin clot directly at the site of vascular injury, both dependently and independently of TF. This reaction provides an extremely strong activation of thrombin at the site of tissue damage, leading to the formation of a stable fibrin network. Administration of rFVIIa might result in formation of a more stable hemostatic plug by a variety of mechanisms, including enhancement of activation of thrombin activatable fibrinolysis inhibitor, improvement of the physical properties of the fibrin clot, enhancement of platelet activation, and possibly enhancement of FXIII activation.

Lisman and colleagues observed that the enhanced thrombin generation from FVIIa not only accelerates clot formation, but also inhibits fibrinolysis by activation of thrombin activatable fibrinolytic inhibitor (TAFI) in factor VIII-deficient plasma. rFVIIa binding to thrombin–activated platelets provides extra thrombin and thus ensures both full activation of TAFI and FXIII, and the formation of a dense fibrin structure. The full thrombin burst generated converts fibrinogen into a firm plug that is resistant to premature lysis, thereby facilitating full hemostasis.

**MONITORING THE CLINICAL EFFECT OF rFVIIa**

Currently, there is no good and/or satisfactory laboratory method for monitoring the clinical effectiveness of rFVIIa. Administration of rFVIIa results in shortening of the prothrombin time (PT) and the activated partial thromboplastin time (APTT). The PT generally shortens to around 7–8 s except in FV- or FX-deficient plasma, suggesting that patients completely deficient in FV and/or FX will not benefit from therapy with this product. PT may not adequately reflect coagulation function. The APTT shortening is due to the direct activation of FX by circulating FVIIa on the phospholipids used in the partial thromboplastin time test. Data indicate that clinical improvement during rFVIIa treatment is associated with a shortening of APTT of 15–20 s. Post-rFVIIa coagulation parameters normalize as early as 20 min after infusion. Thus, the shortening of these two screening tests of coagulation does not necessarily reflect clinical effectiveness, which is judged subjectively.

Coagulopathy is usually easy to recognize by the clinical assessment of ongoing bleeding, physical examination and observation of oozing from cut surfaces, intravascular catheter sites or mucus membranes. The initial evaluation during hemorrhage includes the PT, APTT, thrombin time (TT) and fibrinogen concentration, antithrombin and platelet count. In the interpretation of these tests, it is important to know the normal range and to be aware of the sensitivity of the screening tests for each coagulation factor, as these
vary from laboratory to laboratory. In addition, assays of clotting parameters may provide different results with different reagents, although these parameters do not show a direct correlation to the level of hemostasis achieved. Finally, it is important to remember that laboratory coagulation parameters may be used as an adjunct to the clinical evaluation of hemostasis for monitoring the effectiveness and treatment schedule of rFVIIa.

Clotting parameters obtained prior to rFVIIa administration are often outside the normal range, perhaps indicating the development of dilutional or consumption coagulopathy in these patients. Post rFVIIa, clotting parameters improve, but do not normalize, and thus cannot be used as predictors of rFVIIa efficacy.

Laboratory monitoring of the efficacy of rFVIIa treatment is helpful. The effect on PT is particularly marked, but this does not always translate to clinically improved blood coagulation. Similarly, measurement of the level of FVII in plasma does not correlate with clinical efficacy. Study of the effects of rFVIIa on monitoring plasma FVIIa levels demonstrates a linear relationship between the concentration of FVIIa and FVII:C (functional clotting ability), but the therapeutic concentration range for FVIIa has not yet been established. The use of plasma FVIIa levels is controversial, and is not an assay that is widely available.

Levels of functional fibrinogen and antithrombin do not change during repeated injections of rFVIIa for the treatment of hemorrhage. The minimal changes that occur postoperatively are not greater than those seen with patients who do not have coagulation disorders. Nonetheless, it is still advisable to monitor patients at risk of systemic activation.

Telgt and colleagues showed that low concentration of rFVIIa, in the absence of TF, can activate FX as assayed by the PT. Higher concentration of rFVIIa had no additional effect on the PT. At rFVIIa doses well below the clinically therapeutic dose, a maximum shortening of the PT occurs. Thus, at doses in the clinically therapeutic range, no further effect on the PT is observed. This suggests that, at concentrations typical for clinical use, tests based on the PT are not useful for monitoring the effect of rFVIIa. Telgt and colleagues, in an experimental study, observed that rFVIIa effectively reduced PT and APTT in normal and deficient (FVIII, FIX, FXI, FXII) plasma. This reduction of both parameters (PT and APTT) has been attributed to the ability of rFVIIa to directly activate FX, even in the absence of TF.

The best available indicator of rFVIIa efficacy is the arrest of hemorrhage judged by visual evidence, hemodynamic stabilization and reduced demand for blood components. There is currently no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa.

SAFETY OF rFVIIa

The complex coagulopathy and high complication rates seen in patients with intractable postpartum hemorrhage, together with the understanding of the localized mechanism of action of rFVIIa, and the low risk of thromboembolic complications following administration of the drug both in animal models and in clinical use, all suggest that rFVIIa is a useful adjunctive therapy for control of severe postpartum hemorrhage. Recombinant FVIIa is a manufactured product, does not contain any human plasma components, and therefore is free from viral contamination. Neither albumin nor any other human protein is used in its manufacturing process. This means that there is no risk of transmission of human viruses or prions. Strict quality control standards are applied to the fermentation process as well as the subsequent extensive purification measures. Genetic recombination eliminates the dependency on donors and allows for the production of unlimited amounts of the medication.

Safety analyses demonstrate that rFVIIa is associated with very few treatment-related adverse events and is very well tolerated. Thus, experience with recombinant factor VIIa in several thousand patients has shown that the incidence of non-serious adverse events is 13% and serious adverse events are less than 1%.

Aledort calculated that the risk of rFVIIa-related thrombosis is 25 per 10⁵ infusions. Despite the mechanism of action, use of rFVIIa in DIC and sepsis remains controversial. Several reports suggest that rFVIIa may be used safely in such situations, without induction of thrombotic complications or when conventional replacement therapy with fresh frozen plasma and red blood cell concentrates fails to provide a hemostatic response. Non-serious side-effects are rarely seen during treatment with recombinant factor VIIa; the most common being pain at the infusion site, fever, headache, vomiting, changes in the blood pressure and skin-related hypersensitivity reactions. Adverse events have not been related to dose.

OUR EXPERIENCE

Between 2000 and 2006 in the Department of Gynecology and Obstetrics, University of Medical Sciences, Poznań we used rFVIIa in almost 45 cases of postpartum hemorrhage. According to data gathered from other areas of Poland, we estimate that it has been used in approximately 100 cases of postpartum hemorrhage.

The data presented below concern our first 18 patients in whom rFVIIa was used. Detailed information is presented in Tables 2–5. Our patient data were obtained when we were using a study protocol and were prepared to use the drug. This was not always the case in other centers (see Table 6).

Recombinant FVIIa was administered intravenously at doses of 16.6–48 µg/kg. In most cases, single administration of rFVIIa was sufficient. However, in severe coagulopathy coexisting with postpartum hemorrhage or prolonged periods of treatment (transfusions, complications of shock) and recurrent bleeding, a second dose similar to the initial dose was necessary to control the bleeding.
Table 2  Clinical details of patients with severe, recurring and uncontrollable bleeding post-delivery

| Number of postpartum hemorrhages | 18 |
| Cause of bleeding/complications |  |
| Uterine atony | 8 |
| Genital tract trauma | 1 |
| Disseminated intravascular coagulation | 8 |
| Shock | 18 |
| Reoperations before rFVIIa administration | 7 |
| Obstetric hysterectomy* | 2 |

*In six cases, hysterectomy was not performed. rFVIIa was administered after the decision to operate was made due to uncontrolled, life-threatening bleeding. After its administration, the bleeding stopped and the operation was not necessary. In two women, hysterectomy was performed in another hospital, before the patients were transported to our department.

Table 3  Blood loss before and after rFVIIa administration

| Blood loss | Median (range) (ml) |
| Before rFVIIa | 3000 (1800–6800) |
| After rFVIIa | 0.00 (0–350) |

Table 4  Transfusion needed before and after rFVIIa administration

| Blood products | Median (range) U/P | Median (range) U/P |
| Red blood cell (IU) | 6 (3–13) | 6 (0–9) |
| Fresh frozen plasma (IU) | 4 (1–8) | 2 (0–9) |

U/P, units per patient

Table 5  Selected laboratory tests before and after rFVIIa administration. Data are given as median (range)

| Parameter | Normal range | Before rFVIIa | 2 hours after rFVIIa | 4 hours after rFVIIa | 12 hours after rFVIIa |
| PT (s) | 11.5–13.5 | 17.35 | 11.10 | 11.25 | 12.65 |
| | (11.9–26.7) | (9.1–18.3) | (9.1–17.6) | (11.2–17.1) |
| APTT (s) | 25–37 | 35.00 | 35.00 | 36.80 | 39.10 |
| | (26–81) | (26–76) | (22–69) | (24–60) |
| PLT (Gpt/l) | 140–440 | 76.50 | 70.00 | 69.50 | 70.50 |

PT, prothrombin time; APTT, activated partial thromboplastin time; PLT, platelets

Conclusions

The analysis of our data clearly shows that rFVIIa was an effective hemostatic drug, which significantly decreased bleeding and led to the rapid stabilization of our patients’ conditions. Clearly, the early use of this agent decreases the amount of transfused preparations. An important secondary observation was the contraction of the uterus after the drug application in patients who had qualified for hysterectomy shortly before the drug was administered. We suggest that rFVIIa should be administered in every case in which embolization of uterine arteries is being considered. Coagulation parameters showed typical shortening of PT and APTT; however, the clinical effect – control of bleeding – was the most important overall effect of the drug. There were no complications of rFVIIa administration. The dose, timing of administration after the diagnosis of postpartum hemorrhage, and the apparent ability to enhance uterine contractility will need further study in the future.

WORLD-WIDE EXPERIENCE

Tables 6–8 present the world-wide experience with rFVIIa in obstetric hemorrhage. The results reported in the literature support the benefit of rFVIIa therapy in obstetric cases with major/life-threatening hemorrhage, even in the presence of disseminated intravascular coagulopathy (DIC)-like ‘coagulopathy’. They demonstrate that rFVIIa is highly effective and safe in allowing quick arrest of life-threatening postpartum hemorrhage unresponsive to conventional treatments. Treatment with rFVIIa led to a reduction in the use of blood products in this relatively large group of patients, decreasing blood product exposure for patients and sparing an expensive and limited resource. Administration of rFVIIa should be also considered before hysterectomy and as an adjunct to invasive/surgical procedures, before they are undertaken. This is particularly true in patients who wish to preserve fertility.

Conclusions

Randomized controlled studies are required to determine the optimal dose and dose schedule of rFVIIa for intractable postpartum hemorrhage and to investigate whether the need for hysterectomy/surgical procedures and overall morbidity rates can be reduced by earlier treatment with higher doses of rFVIIa. In the meanwhile, clinicians caring for acutely bleeding obstetric patients should be aware of the potential of rFVIIa to arrest life-threatening postpartum hemorrhage. Although an expensive product, a trial of one to four doses of rFVIIa can be justified in cases of uncontrolled bleeding which persists despite maximal medical and surgical treatment to achieve hemostasis.

Although the limitations of anecdotal case data are recognized, in the absence of efficacy and safety data from randomized trials, voluntary registry submissions are being used to provide a preliminary insight into the scope of the low incidence of clinical problems, as well as the usefulness and adverse effects of this medication when it is used ‘off-label’.

rFVIIa dose

When a rationale for using rFVIIa was stated, it was most commonly ‘last-resort’ therapy, after other clinical measures had failed. There was no clear correlation between the severity of bleeding and the dose of rFVII administered. Possibly the ‘timing’ determined the level of the dosing.
Efficacy

Bleeding either stopped, markedly decreased or decreased following rFVIIa administration in 54 of the cases. In one patient, there was no response to therapy with rFVIIa. Also only in one patient after an early significant reduction of bleeding, recurrence was observed. In general, however, the rapid onset of action means that rFVIIa can be used in the perioperative period. There was no clear correlation between the speed of response and either the type of procedure performed, the severity of the bleeding condition, or the dose of rFVIIa given.

Most patients continued to require some form of blood product replacement therapy during the 24 h following rFVIIa administration, but the need was greatly reduced compared with the 24 h prior to rFVIIa administration. No correlation existed between baseline and post-rFVIIa administration in laboratory measurements and the predictability of response to rFVIIa (data obtained from references but not presented in tables). Furthermore, of great importance, the results observed in these tables of cases of postpartum hemorrhage suggest that rFVIIa may be administered even in the presence of DIC-like 'coagulopathy'. In the patients shown in Tables 6–8, major conditions reported to be associated with postpartum hemorrhage included some individuals with HELLP syndrome and others with both laboratory and clinical signs of DIC before rFVIIa was administered. However, none of these patients developed an objectively confirmed, clinically manifest thromboembolism (deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular embolism) after rFVIIa therapy, even if some patients had pre-existing signs of DIC (often severe).

Patients with HELLP syndrome who develop DIC are recognized as being at particular risk for life-threatening complications. The HELLP syndrome is a form of severe pre-eclampsia, and may be confused with the development of DIC. Data presented in Tables 6–8 suggest a high efficacy and safety profile of rFVIIa in the treatment of HELLP syndrome and/or DIC with massive bleeding. These findings are supported by clinical experiences about the therapeutic effectivity of rFVIIa in three patients with massive obstetric hemorrhage due to placenta previa, accreta, rupture of the uterus and pre-eclampsia with HELLP recently published by an Israeli group. As mentioned by Segal and colleagues, these results raise the possibility that rFVIIa may be administered in obstetric cases with life-threatening bleeding episodes, even in the presence of DIC-like coagulopathy. Injection of rFVIIa should be also considered before hysterectomy in a young patient with severe bleeding, or after internal iliac artery ligation, if bleeding continues.

The series of patients reported here provides data on the safety and efficacy of rFVIIa in intractable early postpartum hemorrhage. However, as with any case series, there are difficulties in data analysis because data were collected retrospectively after the bleeding episode had occurred.

Safety

Adverse thromboembolic events were reported in one case that was considered to be directly related to the use of rFVIIa. In general, rFVIIa administration was associated with an excellent safety profile.

PROPOSAL OF RECOMMENDATION FOR THE USE OF rFVIIa IN SEVERE POSTPARTUM HEMORRHAGE

Based on our own experience and data from the literature, we have prepared guidelines for treatment of postpartum hemorrhage that include administration of rFVIIa.

Definitions of severe hemorrhage

1. Loss of entire blood volume within 24 h;
2. Loss of 50% of blood volume within 3 h;
3. Blood loss at a rate of 150 ml/min (for 20 min $>50%$ blood volume);
4. Blood loss at a rate of 1.5 ml/kg/min for $\geq 20$ min;

Definition of insufficient standard management

The hemorrhage continues despite:
1. All standard pharmacological and surgical treatment methods have been used;
2. Replacement therapy was performed;
3. Coagulopathy was confirmed by laboratory testing
   a. PT or APTT $>1.5$ times the control value
   b. Thrombocytopenia $<50 \times 10^9$/l
   c. Fibrinogen $<0.6–0.8$ g/l.

Preconditions for rFVIIa administration

1. Hematological parameters
   a. Hemoglobin levels $>70$ g/l (4.3 mmol/l)
   b. International normalized ratio (INR) $<1.5$
   c. Fibrinogen levels $\geq 1$ g/l
   d. Platelets levels $\geq 50 \times 10^9$/l
2. pH correction ($\geq 7.2$) (suggest using NaHCO$_3$)
3. Body temperature should be restored if possible to physiological values: rFVIIa retains its activity in the presence of hypothermia.

Correction of the pH to $\geq 7.2$ is recommended before rFVIIa administration (efficacy of rFVIIa decreases at a pH $\leq 7.1$). We also suggest using bicarbonate to elevate the serum pH. It should be noted that NaHCO$_3$ has...
<table>
<thead>
<tr>
<th>Year</th>
<th>Ref.</th>
<th>n</th>
<th>Provenance of bleeding</th>
<th>Type of delivery</th>
<th>Surgical treatment</th>
<th>Blood products given pre-rFVIIa (units)</th>
<th>Overall bleeding response to rFVIIa (min)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>47</td>
<td>1</td>
<td>DIC, liver dysfunction, renal failure, severe maternal abdominal bleeding after CS</td>
<td>CS</td>
<td>NA</td>
<td>&gt;3000</td>
<td>Post hysterectomy; last resort</td>
<td>90 (9) 3-h intervals</td>
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<tr>
<td>2002</td>
<td>48</td>
<td>1</td>
<td>Congenital FVII deficiency</td>
<td>VD</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>49</td>
<td>1</td>
<td>Acquired hemophilia (FVIII 0.5%)</td>
<td>VD</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>50</td>
<td>1</td>
<td>2-h post CS massive vaginal bleeding, shock, DIC, HELLP</td>
<td>CS</td>
<td>RBC (65); FFP (60); CRYO (50); vWF (100); FIX (30); PPTs (8); CRYO (50); CRYO (50)</td>
<td>NA</td>
<td>Bleeding stopped (rapidly)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>51</td>
<td>1</td>
<td>Bleeding from the placenta bed in lower uterine segment and cervical canal</td>
<td>CS</td>
<td>Under-running sutures in the placenta bed; application of hot packs; direct manual tamponade with surgical gauze; insertion of intra-cervical Foley’s catheter balloon</td>
<td>RBC (1.5); FFP (500 ml)</td>
<td>&gt;3000</td>
<td>Post laparotomy; 2-h interval, 2-d interval, before planned hysterectomy</td>
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<td>2003</td>
<td>52</td>
<td>2</td>
<td>(case 1) uterine rupture, shock</td>
<td>IVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>53</td>
<td>1</td>
<td>Uterine atony, shock</td>
<td>IVD</td>
<td></td>
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Table 6: Clinical characteristics of patients with risk of severe, recurring and uncontrollable blood loss during delivery and postpartum: literature review
<table>
<thead>
<tr>
<th>Year</th>
<th>Case</th>
<th>Condition</th>
<th>Intervention</th>
<th>Complications</th>
<th>Treatment</th>
<th>Other Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>54</td>
<td>Uterine atony, pre-eclampsia</td>
<td>CS</td>
<td>HYS</td>
<td>RBC (3); FFP (2); CRYO (6)</td>
<td>NA</td>
</tr>
<tr>
<td>2003</td>
<td>55</td>
<td>AFE, DIC</td>
<td>CS</td>
<td>HYS, pelvic packing</td>
<td>RBC (12); FFP (8); (aprotinin)</td>
<td>NA</td>
</tr>
<tr>
<td>2003</td>
<td>56</td>
<td>Uterine rupture; shock; DIC</td>
<td>IVD</td>
<td>3 laparotomy: 1st: HYS; 2nd: packing of pelvic; 3rd: small arteries ligated in the broad ligaments</td>
<td>Before 1st administration: RBC (26); FFP (11); PPTs (10); PCC (1200). Total: RBC (27); FFP (27); PPTs (10); 22 platelepheresis; (tranexamic acid)</td>
<td>4000 to 2nd laparotomy; before 3rd laparotomy</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Year</th>
<th>Ref.</th>
<th>n</th>
<th>Provocation of bleed</th>
<th>Type of delivery</th>
<th>Surgical treatment</th>
<th>Blood products given pre-rFVIIa (units)</th>
<th>Blood lost before rFVIIa (ml)</th>
<th>Timing when rFVIIa given</th>
<th>Dose of rFVIIa (µg/kg)</th>
<th>Overall bleeding response to rFVIIa</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>58</td>
<td>2</td>
<td>Uterine atony, shock, severe coagulopathy</td>
<td>(case 1) CS (case 2) CS</td>
<td>(case 1) ligation of hypogastric arteries; (case 2) ligation of hypogastric arteries</td>
<td>(case 1) RBC (19); FFP (3350 ml); PPTs (900 ml); fibrinogen (3 g); aprotinin</td>
<td>(case 1) 200 ml/h; (case 2) 2000 ml, hemo-peritoneum</td>
<td>Last resort (case 1)</td>
<td>(case 1) 60 (case 2) 60</td>
<td>Bleeding stopped (rapidly)</td>
<td>(case 1) 4 weeks later developed thrombosis of both ovarian veins</td>
</tr>
<tr>
<td>2004</td>
<td>59</td>
<td>1</td>
<td>Placenta previa; accreta; DIC</td>
<td>CS</td>
<td>No</td>
<td>RBC (11); FFP (4); CRYO (6)</td>
<td>1000 (in the drain) 5 h after CS</td>
<td>12 mg</td>
<td>Bleeding stopped (few hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>60</td>
<td>1</td>
<td>Glanzmann’s thrombasthenia</td>
<td>VD</td>
<td>No</td>
<td>PPTs (4)</td>
<td>No evidence of bleeding</td>
<td>Prophylactic</td>
<td>36 (2) 1st during vaginal delivery, 2nd 2 h after delivery</td>
<td>800 ml (intra- and postpartum blood loss)</td>
<td>rFVIIa may offer an alternative option in patients with Glanzmann’s thrombasthenia during delivery</td>
</tr>
<tr>
<td>2004</td>
<td>61</td>
<td>1</td>
<td>AFE; DIC (developed 2 min after delivery)</td>
<td>CS</td>
<td>No</td>
<td>RBC (6); FFP (1); PPTs (2)</td>
<td>3000</td>
<td>90</td>
<td>Hemostasis was secured within 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>62</td>
<td>3</td>
<td>(case 1) Eclampsia; HELLP; consumptive coagulopathy; subcapsular liver hematoma with capsule rupture (case 2) placenta percreta, pre-eclampsia; HELLP (case 3) pre-eclampsia; HELLP; placenta accreta; consumptive coagulopathy; severe vaginal bleeding and uterine cramping</td>
<td>(case 1) CS (case 2) CS (case 3) CS</td>
<td>No</td>
<td>(case 1) RBC (16); FFP (14); PPTs (8); CRYO (10) (case 2) RBC (8); FFP (4); PPTs (6) (case 3) RBC (2); FFP (4); PPTs (6); CRYO (10)</td>
<td>(case 1) 2500 (case 2) 3000 (case 3) 1300</td>
<td>Last resort (case 1)</td>
<td>(case 1) 90 (2) 2 h interval</td>
<td>Bleeding controlled (case 1)</td>
<td>(case 1) patient developed anuric renal failure; cardiac arrest; patient died; no evidence of systemic thrombosis identified (case 2) no future transfusion requirement; coagulation profile stabilized</td>
</tr>
<tr>
<td>Year</td>
<td>Case</td>
<td>Conditions</td>
<td>Intervention</td>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004 63</td>
<td>1</td>
<td>Pre-eclampsia; HELLP; DIC, shock</td>
<td>Laparotomy 12 h after CS, because intra-abdominal hemorrhage</td>
<td>Bleeding reduced (30), Bleeding stopped (180)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 64</td>
<td>3</td>
<td>(case 1) Uterine atony, shock; (case 2) placenta previa, uterine atony; (case 3) laceration of vagina, atony, consumptive coagulopathy</td>
<td>Relaparotomy with intracavitary oxytocin injected into the uterus; ligation of both uterine arteries; placement of B-Lynch sutures</td>
<td>NA</td>
<td>Improves coagulation parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 65</td>
<td>1</td>
<td>Uterine atony, shock; DIC</td>
<td>HYS, packing of the pelvis</td>
<td>NA</td>
<td>Before relaparotomy and ligation hypogastric artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 66</td>
<td>4</td>
<td>Uterine atony</td>
<td>Vaginal delivery</td>
<td>NA</td>
<td>Before developed severe coagulopathy, surgical procedures; avoided massive transfusion</td>
<td>Bleeding controlled (rapid response)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005 67</td>
<td>3</td>
<td>(case 1) dehiscence of uterine scar; (case 2) placenta percreta, adherent; dehiscence of uterine scar (previous CS)</td>
<td>(case 1) eCS</td>
<td>Bleeding controlled (16)</td>
<td>Lower than standard doses may be effective when respect good timing, before complication develops</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- RBC: red blood cell concentrates; FFP: fresh frozen plasma; PPTs: platelets; CRYO: cryoprecipitates; WB: whole blood; PCC: prothrombin complex concentrate; vWF: von Willebrand factor; CS: cesarean section (e, emergency); VD: vaginal delivery; IVD: instrumental vaginal delivery; DIC: disseminated intravascular coagulation; MOF: multiple organ failure; NA: not available; HYS: hysterectomy; laceration – uterine or vaginal; AFE: amniotic fluid embolism; HELLP: hemolysis, elevated liver enzymes, low platelets; ’last resort’, therapy, after other clinical measures had failed; n, number of cases
Table 7  Patients with severe postpartum hemorrhage, presented by Ahonen and colleagues (2005)68. The authors concluded that treatment with rFVIIa may be of benefit in life-threatening postpartum hemorrhage of up to 20 l of blood in 5–8 h. For comments on this article, see reference 69

<table>
<thead>
<tr>
<th>Case</th>
<th>Provocation of bleed</th>
<th>Type of delivery</th>
<th>Additional surgeries (number of surgery)</th>
<th>Blood products given pre-rFVIIa (units)</th>
<th>Blood loss before rFVIIa (l)</th>
<th>Timing (when rFVIIa administered)</th>
<th>Dose of rFVIIa (µg/kg) (number of doses)</th>
<th>Overall bleeding response to rFVIIa (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placenta accreta</td>
<td>VD</td>
<td>HYS</td>
<td>RBC (42); FFP (25); PPTs (40)</td>
<td>25.0</td>
<td>After HYS</td>
<td>44 (1)</td>
<td>Partial</td>
</tr>
<tr>
<td>2</td>
<td>Adherent placenta</td>
<td>CS</td>
<td>HYS</td>
<td>RBC (38); FFP (14); PPTs (24)</td>
<td>20.0</td>
<td>After HYS</td>
<td>95 (4)</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>Uterine atony, LAC</td>
<td>VD</td>
<td>Surgery (3)</td>
<td>RBC (19); FFP (8); PPTs (8)</td>
<td>11.0</td>
<td>Before HYS</td>
<td>78 (1)</td>
<td>Good</td>
</tr>
<tr>
<td>4</td>
<td>Laceration</td>
<td>VD</td>
<td>Surgery (2), embolization</td>
<td>RBC (25); FFP (16); PPTs (24)</td>
<td>14.0</td>
<td>NA</td>
<td>103 (5)</td>
<td>Partial</td>
</tr>
<tr>
<td>5</td>
<td>Laceration</td>
<td>CS</td>
<td>HYS (3 laparotomy)</td>
<td>RBC (32); FFP (20); PPTs (40)</td>
<td>19.0</td>
<td>After HYS</td>
<td>90 (4)</td>
<td>Good</td>
</tr>
<tr>
<td>6</td>
<td>Uterine atony</td>
<td>CS</td>
<td>Surgery, embolization</td>
<td>RBC (10); FFP (8); PPTs (16)</td>
<td>5.5</td>
<td>NA</td>
<td>116 (10)</td>
<td>Partial</td>
</tr>
<tr>
<td>7</td>
<td>Placenta accreta</td>
<td>VD</td>
<td>HYS</td>
<td>RBC (14); FFP (6); PPTs (4)</td>
<td>7.5</td>
<td>After HYS</td>
<td>42 (2)</td>
<td>Partial</td>
</tr>
<tr>
<td>8</td>
<td>Laceration</td>
<td>CS</td>
<td>Surgery (2), right uterine artery ligation</td>
<td>RBC (11); FFP (4); PPTs (8)</td>
<td>5.3</td>
<td>NA</td>
<td>120 (1)</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Placenta percreta</td>
<td>CS</td>
<td>HYS (2)</td>
<td>RBC (25); FFP (14); PPTs (16)</td>
<td>14.0</td>
<td>After HYS</td>
<td>77 (3)</td>
<td>Good</td>
</tr>
<tr>
<td>10</td>
<td>Laceration</td>
<td>IVD</td>
<td>Surgery, embolization</td>
<td>RBC (13); FFP (10); PPTs (32)</td>
<td>8.8</td>
<td>NA</td>
<td>74 (2)</td>
<td>Partial</td>
</tr>
<tr>
<td>11</td>
<td>Laceration</td>
<td>VD</td>
<td>Surgery</td>
<td>RBC (11); FFP (6); PPTs (6)</td>
<td>5.5</td>
<td>NA</td>
<td>86 (1)</td>
<td>Good</td>
</tr>
<tr>
<td>12</td>
<td>Laceration</td>
<td>VD</td>
<td>Surgery, embolization</td>
<td>RBC (10); FFP (8); PPTs (16)</td>
<td>5.8</td>
<td>NA</td>
<td>96 (1)</td>
<td>Partial</td>
</tr>
</tbody>
</table>

RBC, red blood cell concentrates; FFP, fresh frozen plasma; PPTs, platelets; CS, cesarean section (e, emergency); VD, vaginal delivery; IVD, instrumental vaginal delivery; DIC, disseminated intravascular coagulation; MOF, multiple organ failure; NA, not available; HYS, hysterectomy; laceration – uterine or vaginal; AFE, amniotic fluid embolism; HELLP, hemolysis, elevated liver enzymes, low platelets; ‘last resort’, therapy, after other clinical measures had failed.
### Table 8  Patients with severe postpartum hemorrhage presented by Segal and colleagues²⁷¹

<table>
<thead>
<tr>
<th>Case</th>
<th>Provocation of bleed</th>
<th>Type of delivery</th>
<th>Additional surgeries</th>
<th>Blood products given pre-rFVIIa (units)</th>
<th>Blood loss before rFVIIa (l)</th>
<th>Timing (when rFVIIa administered)</th>
<th>Dose of rFVIIa (µg/kg) (number of doses)</th>
<th>Overall bleeding response to rFVIIa (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placenta accreta</td>
<td>CS</td>
<td>HYS; ligation of internal iliac arteries; packing</td>
<td>RBC (44); FFP (24); PPTs (60); CRYO (54)</td>
<td>NA</td>
<td>NA</td>
<td>90 (2)</td>
<td>Bleeding stopped</td>
</tr>
<tr>
<td>2</td>
<td>Uterine rupture</td>
<td>VD</td>
<td>HYS; ligation of internal iliac arteries</td>
<td>RBC (20); FFP (16); PPTs (60); CRYO (60)</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>Bleeding stopped</td>
</tr>
<tr>
<td>3</td>
<td>Uterine atony</td>
<td>CS</td>
<td>CS, packing of uterus; laparotomy; packing of tears on liver</td>
<td>RBC (19); FFP (8); PPTs (8)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding reduced</td>
</tr>
<tr>
<td>4</td>
<td>Uterine atony</td>
<td>NA</td>
<td>Subtotal HYS; ligation of internal iliac arteries</td>
<td>RBC (14); FFP (12); PPTs (10); CRYO (10)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding stopped</td>
</tr>
<tr>
<td>5</td>
<td>Uterine rupture</td>
<td>NA</td>
<td>Ligation of internal iliac arteries; subtotal HYS</td>
<td>RBC (26); FFP (16); PPTs (30); CRYO (60)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding stopped</td>
</tr>
<tr>
<td>6</td>
<td>Placenta accreta</td>
<td>NA</td>
<td>Arterial embolization; HYS; iliac ligation; 4 laparotomies; packing</td>
<td>RBC (100); FFP (50); PPTs (50); CRYO (50)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding controlled</td>
</tr>
<tr>
<td>7</td>
<td>Uterine rupture</td>
<td>NA</td>
<td>HYS; ligation of internal iliac arteries; packing</td>
<td>RBC (10); FFP (6); CRYO (4)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding reduced</td>
</tr>
<tr>
<td>8</td>
<td>Uterus myomatus, menorrhagia</td>
<td>NA</td>
<td>HYS</td>
<td>RBC (6); FFP (9)</td>
<td>NA</td>
<td>NA</td>
<td>60</td>
<td>No bleeding</td>
</tr>
<tr>
<td>9</td>
<td>Uterine rupture</td>
<td>NA</td>
<td>HYS</td>
<td>RBC (15); FFP (6); PPTs (15); CRYO (30)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding stopped</td>
</tr>
<tr>
<td>10</td>
<td>Placenta accreta</td>
<td>NA</td>
<td>HYS; ligation of internal iliac arteries; aortic clamp</td>
<td>RBC (27); FFP (30); PPTs (10); CRYO (30)</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
<td>Bleeding stopped</td>
</tr>
</tbody>
</table>

RBC, red blood cell concentrates; FFP, fresh frozen plasma; PPTs, platelets; CRYO, cryoprecipitates; CS, cesarean section; VD, vaginal delivery; NA, not available; HYS, hysterectomy
not been shown to provide benefits to patients in hemorrhagic shock.

Recommended replacement therapy

(1) Fresh frozen plasma: 5–10 ml/kg (4–5 units);
(2) Cryoprecipitates: 1–1.5 units/10 kg (8–10 units);
(3) Platelets: 1 units/10 kg (5–8 units);
(4) Correction of acidosis (defined as pH ≥ 7.2);
(5) Warming of hypothermic patients (recommended, but not mandatory for administration of rFVIIa).

Dosing administration protocol proposal

(1) The recommended initial dose of rFVIIa for treatment of severe postpartum hemorrhage is ~40–60 µg/kg administered intravenously.
(2) If bleeding still continuous beyond 15–30 min, following the first dose of rFVIIa, an additional dose of ~40–60 µg/kg should be considered. Repeat 3–4 times at 15–30-min intervals if clinical signs of bleeding are still present (based on visual evidence).
(3) If the response remains inadequate following a total dose of >200 µg/kg, the preconditions for rFVIIa administration should be re-checked, and corrected as necessary before another dose is considered.
(4) Only after these corrective measures have been applied should the next dose of rFVIIa ~100 µg/kg be administered.

Recommended timing of administration

Because our experience suggests that rFVIIa permits effective control of obstetric bleeding, especially in situations of coexisting coagulopathy, we therefore recommend administration of rFVIIa as soon as possible under the following circumstances:

(1) When no blood is available;
(2) Before metabolic complications develop;
(3) In women refusing transfusions (e.g. Jehovah Witnesses) (see Chapter 72);
(4) In acquired hemophilia (see Chapter 25);
(5) Before the symptoms of severe thrombocytopenias, hypoxia and organ injury appear;
(6) If correction of INR (PT) is urgently needed;
(7) Before packing of the uterus or pelvis;
(8) Before surgical procedures such as hysterectomy, laparotomy;
(9) Before medical procedures such as embolization, ligation of the uterine and internal iliac arteries (see Chapters 52 and 53).

Information obtained from the literature allows us to summarize the advantages and disadvantages of rFVIIa as follows.

Advantages

(1) Recombinant product;
(2) Not subject to blood shortage;
(3) No viral transmission;
(4) No human protein;
(5) Localized hemostasis;
(6) Low risk of anaphylaxis;
(7) No anamnestic responses;
(8) Low thrombogenicity;
(9) Effective during and after surgery.

Disadvantages

(1) Short t1/2 requires frequent, repetitive dosing;
(2) Not 100% effective;
(3) No measurable lab parameter for efficacy;
(4) Limited vial sizes;
(5) Venous access;
(6) Cost.

References

2. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomized trial of two doses of rFVIIa (NovoSeven®) in haemophilia patients undergoing surgery. Thromb Haemost 1998;80:773–8
36. Bąbrorowicz GH, Sobieszczyk S [Usefulness of recombinant active factor VII (rFVIIa, NovoSeven®) in obstetric practice – own experiences]. Przydatność rekombinowanej aktywnego czynnika VIIa (rFVIIa, NovoSeven®) w praktyce położniczej – doświadczenia własne. Klin Perinat Ginek 2001;34:7–12
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