

The Use of Recombinant Activated FVII in Postpartum Hemorrhage

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Abstract: Severe bleeding remains a leading cause of morbidity and mortality in obstetrics. The first-line standard treatment of massive postpartum hemorrhage (PPH) includes medical measures directed at improving uterine tone, replacement of lost intravascular volume, blood and coagulation factors, and surgical or invasive procedures. Recently, a number of case reports or case series have reported the successful “off-label” use of recombinant activated factor VII (rFVIIa) in PPH unresponsive to conventional treat-

ments. In this review, a critical analysis of the published literature on the use of rFVIIa in severe PPH was performed. Overall, a total of 272 PPH women were collected among the largest case series and/or international registries. No randomized controlled trials have been conducted in this area. Currently, the literature data suggest that, at a median dose of 81.5 µg/kg, rFVIIa is effective in stopping or reducing bleeding in 85% of the cases. Finally, on the basis of the evidence from the literature and on own experience, we included some recommendations and an algorithm on the therapeutic role of rFVIIa in the management of PPH.

Key words: postpartum hemorrhage, bleeding, rFVIIa, obstetric

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Introduction

Major postpartum hemorrhage (PPH) is a life-threatening complication of labor, which mostly occurs without any warning, predictive signs and symptoms, and often, in absence of predisposing conditions.¹ Severe PPH, which is traditionally defined as blood loss of ≥ 500 mL after vaginal delivery and ≥ 1000 mL after a caesarean delivery in the first 24 hours postpartum, accounts for nearly one-quarter of all maternal deaths world-wide, with an estimation of 125,000 deaths per year.^{2,3}

Currently, the therapeutic strategies for the management of severe PPH are largely standardized. The cornerstone of massive PPH consists of the administration of uterotonic drugs, infusion of large quantities of colloids-crystalloids and blood components (to replace lost intravascular volume and to restore oxygen-carrying capacity and hemostatic competence), radiologic interventional procedures (uterine or internal iliac arteries embolization), surgical conservative approaches (B-lynch suture with hemostatic intention) and, finally, hysterectomy.⁴ Nonetheless, the rate of PPH-related mortality and morbidity remains unacceptably high in developed countries, being a significant contributing risk factor for hysterectomy in at least 75% of cases.^{5,6}

Various risk factors for peripartum hemorrhage have been identified (ie, prior PPH, advanced maternal age, cesarean delivery, placental abruption, multifetal gestations, multiparity, placenta previa and accreta, instrumental delivery, prolonged labor, etc). However, these risk factors are only of limited utility for the prevention of peripartum hemorrhage.¹ Causes of PPH are usually because of utero-placental defects (uterine atony, pathologic placental implantation, or retained products of conception), birth canal trauma (uterine or vaginal lacerations), and congenital or acquired coagulation disorders. Whatever is the cause of

primary severe PPH, obstetric massive bleeding can be complicated by the so-called "lethal triad": acidosis, hypothermia, and coagulopathy. Therefore, a number of protocols for the management of major bleeding in the obstetric setting have been developed with the aim of preventing and treating these dangerous complications.⁷ Particularly, they have been directed toward the implementation of hemostatic therapies for the management of severe acquired coagulopathy, which is a crucial pathogenic step during the course of life-threatening PPH.⁸⁻¹⁰

In this context, there is an increasing number of case reports describing the successful "off-label" use of recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), a "bypassing" hemostatic agent which was originally developed for the treatment of hemophiliacs with inhibitors,¹¹ in the treatment of massive PPH refractory to conventional medical and surgical therapy.¹² The rationale for the use of rFVIIa in this setting is based on the observation that, at pharmacologic doses, it directly activates factor X on the surface of activated platelets at the site of injury independently of tissue factor, factors VIII and IX. This results in a "thrombin burst" with the conversion of prothrombin into large amounts of thrombin and the local formation of a stable fibrin clot that may control bleeding.¹³

In this systematic review, we critically analyze current data on the use of rFVIIa in PPH to provide practical recommendations for clinicians on the pharmacologic management of obstetric hemorrhage.

Search Methods

A computer-assisted search of the MEDLINE and EMBASE electronic databases up to December 2008 was performed to identify published studies that reported the use of rFVIIa in PPH. The following search terms (medical subject heading

terms and text words) were used for the search: postpartum hemorrhage, obstetric, pregnancy, PPH, bleeding, rFVIIa, eptacog á, and NovoSeven.

Reference lists of all included studies were manually searched for other potentially eligible studies. Unpublished works were identified by searching the abstract books of the most important conferences on obstetric and hematologic diseases.

No randomized studies were found after an electronic and hand search. In addition, as no case-control or interventional cohort studies were reported, a quality assessment approach based on the modified Newcastle-Ottawa scale and the Cochrane Collaboration could not be applied. However, to obtain informative data, only case-reports describing at least 10 cases were included for the analysis of this review.

In total, we identified 124 references through the electronic and hand searches. After reading the full text of the articles, we excluded 68 irrelevant references and

retrieved 56 references for further assessment. A further 16 studies were excluded because they were reviews or duplicates of already included studies. Among the remaining 40 studies with usable information, we included only those reporting more than 10 cases in the final analysis. Thus, we considered 9 studies for this review,¹⁴⁻²² with data on 272 PPH patients (the 31 excluded studies evaluated 57 patients). Figure 1 shows the flow chart of studies included in this chapter.

Results

Although several case reports have been published in the last 8 years on the off-label use of rFVIIa in PPH, it is evident that most of the PPH patients treated with this agent worldwide remain unreported.¹⁸ After the accumulation of reported data, review articles on this topic have been published to extract useful indications for the management of this life-threatening conditions.²³

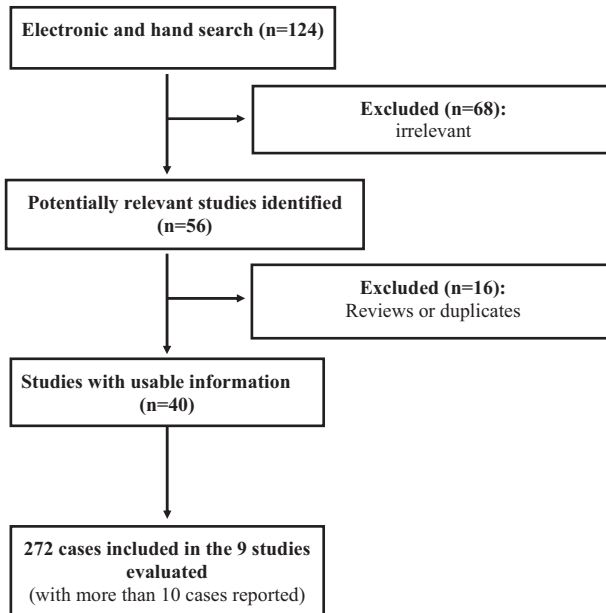


FIGURE 1. Flow chart of inclusion studies.

Among the largest case series published in this area, Ahonen and Jokela¹⁵ presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions and found a good response in 11 (91.7%) of them. Interestingly, the authors recorded a learning curve in the use of rFVIIa for surgeons and anesthetists: in the first part of the study the average use of blood products before the use of rFVIIa was 67.6 units, but only 37.2 units in the second part of the study, indicating that rFVIIa was being administered earlier in the bleeding episodes. The same authors successively published an open, nonrandomized retrospective study where they compared 26 women receiving rFVIIa with 22 women receiving standard treatments.¹⁷ The study found that rFVIIa had only been administered to those women with more severe bleeding and worse coagulopathy compared with control subjects. The response to rFVIIa was considered good in approximately two-thirds of the patients, defined as bleeding ≤ 1000 mL after rFVIIa administration and no requirement for additional interventions, except suturing of vaginal lacerations. In those with poor or no response, the ongoing bleeding was arterial. One patient treated with rFVIIa suffered a pulmonary embolism episode and was subsequently found to have anti-thrombin deficiency. A further study retrospectively identified 34 PPH patients, 18 of whom had received rFVIIa.²⁰ The subjects who had been given rFVIIa had lower maternal mortality (5 of 18, 28% vs. 8 of 16, 50%; $P = 0.09$) and received a lower number of red blood cell (RBC) transfusions (4.0 ± 4.46 vs. 9.61 ± 6.7 , $P = 0.007$), than the control group, despite lower hemoglobin levels ($P = 0.02$) and more severe coagulopathies determined by prothrombin time and activated partial thromboplastin time ($P = 0.03$ and $P = 0.05$, respectively). There was no difference in the rate of hysterectomy

between the 2 groups, and no adverse effects attributable to rFVIIa were identified. Segal and colleagues¹⁴ reported 10 women successfully treated for severe obstetric hemorrhage with 1 or 2 doses of 60 to 100 $\mu\text{g}/\text{kg}$ of rFVIIa. Bouma and colleagues¹⁹ reported 27 PPH cases treated with rFVIIa. Uterine atony was responsible for 82% of PPH cases. At a median dose of 79 $\mu\text{g}/\text{kg}$ (range: 16 to 128 $\mu\text{g}/\text{kg}$), rFVIIa was effective in avoiding emergency hysterectomy in 16 of 21 cases (76%), and led to a relevant reduction or complete cessation of bleeding in 24 of 27 cases (89%).

To give indications on the safety and efficacy of rFVIIa in this setting, a number of international registries have been set up in the last few years. The Northern Europe Factor VIIa in Obstetric Hemorrhage Registry collected data from 9 European countries between 2000 and 2004.¹⁸ Sixty-five of 531 hospitals known to use rFVIIa reported its use in primary PPH in 128 patients; 113 forms were returned (88%), with 97 (86%) classified as treatment (where other interventions had failed) and 16 (14%) as secondary prophylaxis (usage to support other successful interventions). Five treatment cases were excluded because of secondary hemorrhage (4 cases) or disseminated intravascular coagulation (1 case). Improvement (defined as reduced bleeding) was found in 84% of treated patients and in 75% of the secondary prophylaxis group, respectively. Failure to respond (defined as bleeding unchanged or worse) was observed in 15 cases. Most women (88 of 108, 81%) received a single dose only, the most common dose being 90 $\mu\text{g}/\text{kg}$ or less (68 of 75, 91%). Five of the treated women died and 4 suffered from deep vein thrombosis after the treatment (one of these was felt to be unrelated to rFVIIa). One woman in the treatment group sustained a myocardial infarction, although she had suffered a cardiac arrest before the rFVIIa administration.

The Australian and New Zealand Registry considered 694 cases from 37 hospitals reported to the Hemostasis Registry (which collects retrospective and contemporaneous data on all use of rFVIIa at participating institutions for nonhemophiliac patients with critical bleeding).²¹ Obstetric bleeding accounted for 4% (n = 27) of these cases; 68% of patients were deemed to have shown a decrease (n = 12) or cessation (n = 5) in bleeding and 85% of patients survived to 28 days. No adverse events associated with rFVIIa were identified in the obstetric group. The median dose given to all patients was 91 $\mu\text{g}/\text{kg}$ (range: 75 to 103 $\mu\text{g}/\text{kg}$), but it was not possible to determine the mean dose in the subset of obstetric patients from the published data. The Italian Registry on the use of rFVIIa in severe PPH retrospectively collected 35 cases. The prothrombin time and fibrinogen levels significantly increased after rFVIIa administration. In addition, a significant reduction of the median need of RBC, platelet, and plasma transfusions was shown before and after rFVIIa administration. A response to rFVIIa, defined as a decrease in RBC requirements of at least 30% after rFVIIa administration, was observed in 89% of patients. As one nonresponder patient had metabolic acidosis at the time of rFVIIa administration, the authors outlined the importance of determining and correcting pH values, as the efficacy of rFVIIa is poor in the setting of acidosis.²⁴ No drug-related adverse events were documented. Finally, Sobieszczyk et al¹⁶ published a case series including 25 PPH cases from an international internet-based registry. The rFVIIa stopped or decreased the obstetrical bleeding in all but one patient. An ongoing randomized controlled trial conducted in France and Switzerland is currently recruiting PPH patients treated with rFVIIa.²⁵ The group planned to compare its early use before elective surgery or arterial embolization,

to its late use after embolization or surgery, before salvage hysterectomy. Recruitment began in December 2006 and is planned to continue until December 2009.

The largest case series published in the literature are summarized in Table 1. The median age of the patients enrolled in the 9 studies was 31.3 years. Among the 235 deliveries, 121 (51.5%) were by vaginal route and 114 (48.5%) by cesarean section. The most common conditions predisposing/worsening obstetrical hemorrhage were, in order of frequency, uterine atony (114 of 222 cases, 51.3%), uterine or vaginal lacerations (62 of 222 cases, 27.9%), placenta abnormalities (50 of 222 cases, 22.5%), and retained placenta (23 of 222 cases, 10.4%). These results are in line with those published earlier in literature.²³ In all cases, large amounts of blood components were transfused as first-line treatment to restore oxygen-carrying capacity (RBCs) and physiologic hemostasis (fresh-frozen plasma and platelets). In most of PPH patients, rFVIIa was used in addition to standard medical (ie, uterotonic drugs) and surgical (hysterectomy was performed in 43% of the cases) hemostatic interventions. However, when rFVIIa was used before hysterectomy, it was often possible to avoid this invasive surgical procedure, thus sparing reproductive function. At a median dose of 81.5 $\mu\text{g}/\text{kg}$ (range: 10 to 137 $\mu\text{g}/\text{kg}$), the drug was effective in stopping or reducing bleeding in nearly 85% of the PPH cases. Poor response to rFVIIa was mainly attributed to inadequate dosages, unrecognized surgical bleeding, and severe metabolic abnormalities. The median number of doses administered was 1.1 (range: 1 to 3) with a single dose being typical. As regards the safety of rFVIIa in massive PPH, adverse events associated with its use occurred only in 2.5% of the cases. However, the fact that all these complications were thrombotic episodes is of note.²⁶

TABLE 1. The Use of rFVIIa in Postpartum Hemorrhage: Results of the Largest Case Series Studies

| Authors (Reference) | Patients (n) | Age (y)* | Causes | Delivery | Hysterectomy† | rFVIIa (µg/kg)* | | Response‡ | Adverse Events |
|---------------------------------|--------------|--------------|--|---------------|----------------|-----------------|-----------|----------------|--|
| | | | | | | Initial Dose | No. Doses | | |
| Segal et al ¹⁴ | 10 | NR | 3 abnormal placentation, 2 uterine atony, 4 uterine rupture, 1 uterine myomatosis | NR | 9/10 (90.0) | 88.0 (60-100) | 1.1 (1-2) | 10/10 (100) | No |
| Ahonen and Jokela ¹⁵ | 12 | 27.7 (24-37) | 4 abnormal placentation, 2 uterine atony, 6 uterine/vaginal lacerations | 5 CS, 7 VD | 5/12 (45.5) | 85.1 (42-120) | 1 | 11/12 (91.7) | No |
| Sobieszcyk et al ¹⁶ | 25 | 30 (23-44) | 2 uterine myomatosis, 23 NR | 16 CS, 9 VD | 13/25 (52.0) | 32.2 (10-137) | 1.2 (1-2) | 24/25 (96.0) | No |
| Ahonen et al ¹⁷ | 26 | 33 + 4 | 3 abnormal placentation, 9 uterine atony, 9 uterine lacerations, 5 retained placenta | 10 CS, 16 VD | 8/26 (30.8) | 100 (73-122) | NR | 20/26 (76.9) | 1 pulmonary embolism§ |
| Alfirevic et al ¹⁸ | 92 | NR | 21 abnormal placentation, 52 uterine atony, 27 uterine/vaginal lacerations, 5 infection, 17 retained placenta, 7 other | 46 CS, 46 VD | 33/92 (35.9) | 90 | 1.2 (1-3) | 77/92 (83.7) | 4 venous thrombo-embolism myocardial infarction 1 pulmonary embolism |
| Bouma et al ¹⁹ | 27 | NR | 22 uterine atony, 5 abnormal placentation, 7 uterine/vaginal lacerations | 8 CS/ 19 VD | 11/27 (40.7) | 79 (16-128) | NR | 24/27 (88.9) | 1 pulmonary embolism |
| Hossain et al ²⁰ | 18 | 29.0 (26-32) | 6 uterine atony, 6 abnormal placentation, 3 uterine/vaginal lacerations, 3 other | 10 CS/8 VD | 11/18 (61.1) | 70 | 1 | 16/18 (88.9) | No |
| Isbister et al ²¹ | 27 | NR | NR | NR | NR | 91 (75-103) | NR | 17/27 (63.0) | No |
| Barillari et al ²² | 35 | 34.5 (23-43) | 21 uterine atony, 6 uterine/vaginal lacerations, 19 CS/16 VD 1 retained placenta, 8 abnormal placentation | 19 CS/16 VD | 20/35 (57.1) | 87.5 (15-127) | 1.2 (1-2) | 31/35 (88.6) | No |
| Total | 272 | 31.3 (23-44) | | 114 CS/121 VD | 110/255 (43.1) | 81.5 (10-137) | 1.1 (1-3) | 240/282 (85.1) | 7/282 (2.5) |

* Median (range) or mean ± SD.

† Number (percentage).

‡ Defined as cessation or significant reduction of bleeding.

§ One patient treated with rFVIIa suffered a pulmonary embolism and was subsequently found to have antithrombin deficiency.

|| Three patients received an additional rFVIIa dose.

CS indicates cesarean section; NR, not reported; rFVIIa, recombinant activated factor VII; VD, vaginal delivery.

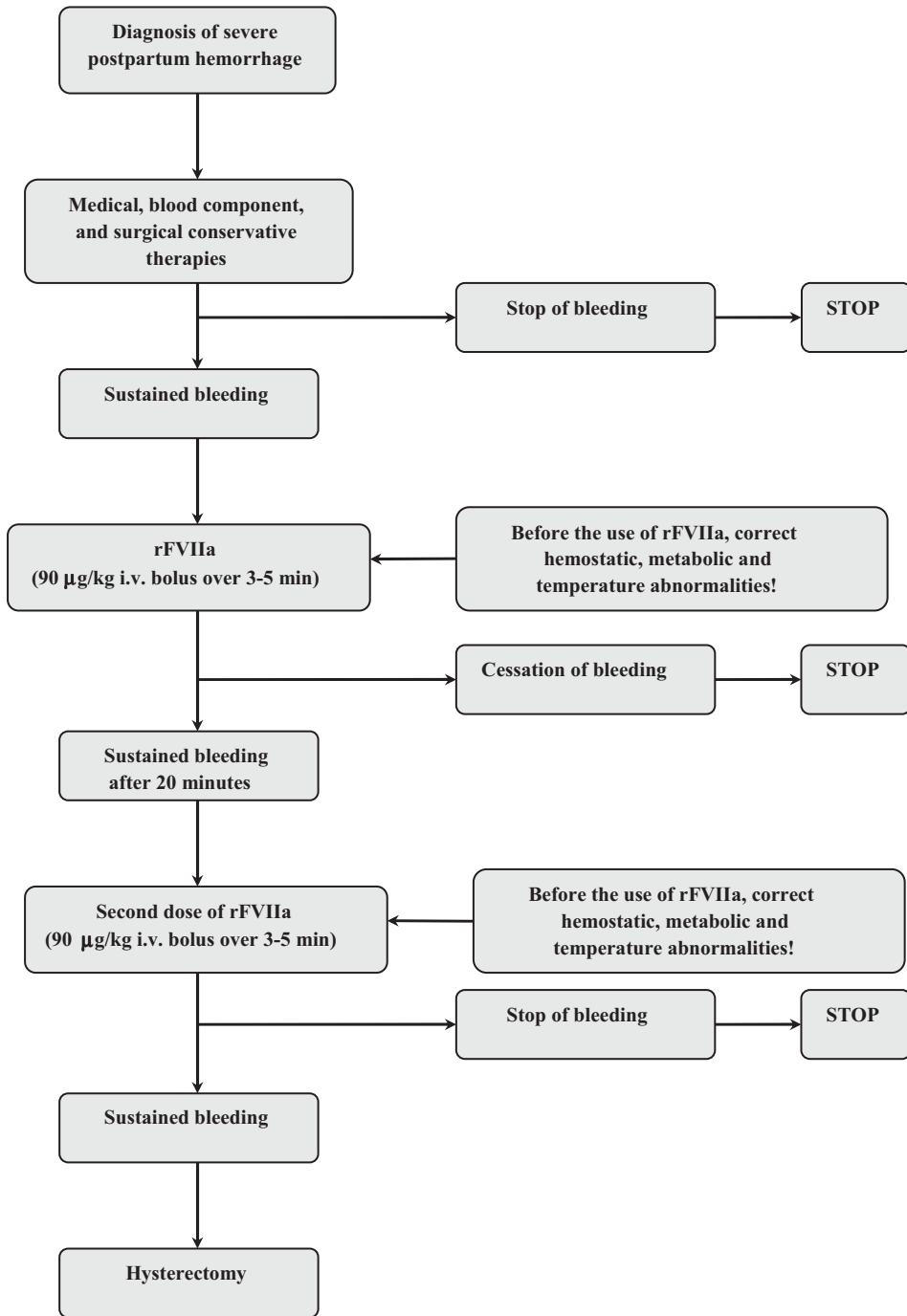


FIGURE 2. Flow diagram on the potential role of recombinant activated factor VII (rFVIIa) in the treatment of postpartum hemorrhage.

Final Recommendations

In conclusion, although limited, the clinical results extracted from the largest published studies, suggest a potential beneficial role of rFVIIa in the management of severe PPH refractory to standard treatment.

Our recommendations on the management of PPH with this agent are the following:

- Consider the use of rFVIIa only after the failure of medical (treatment of hemodynamic instability, hypothermia, and metabolic abnormalities; uterine massage/compression; and uterotonic agents), blood component (transfusion of RBC, platelet, and fresh-frozen plasma to correct anemia, thrombocytopenia, and coagulopathy), and conservative surgical/invasive (B-Lynch suture, internal iliac or uterine artery ligation, internal uterine tamponade, and uterine artery radiologic embolization) therapies.
- Administer rFVIIa 90 µg/kg as an intravenous bolus over 3 to 5 minutes.
- Before the rFVIIa injection, check that all abnormal parameters influencing rFVIIa efficacy (ie, acidosis, thrombocytopenia, hypofibrinogenemia, hypothermia, and hypocalcemia) have been corrected.
- If, 20 minutes after the first dose of rFVIIa, there is no response, administer a second dose of rFVIIa (90 µg/kg), ensuring before that temperature, acidemia, serum calcium, platelets, and fibrinogen have been optimized.
- If bleeding persists after 2 doses of rFVIIa, consider hysterectomy.

Figure 2 reports our suggested flow-chart on the potential role of rFVIIa in the management of PPH. We must outline that this flow chart is based on our personal experience supplemented by the literature review. However, the value of available data is limited by the retrospective nature of the studies and small patient numbers. Indeed, no randomized, placebo-controlled trials have been conducted so far on the use of rFVIIa in obstetric hemorrhage. However, it is unlikely that such a trial will be ever performed because of the rarity and the emergency situation

of this condition and, most importantly, because of the extremely positive results, both in terms of efficacy and safety, reported in the published literature. Further, properly conducted trials are needed to assess how and when rFVIIa should be used in PPH.

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