

The use of recombinant activated factor VII in life-threatening postpartum hemorrhage

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SUMMARY

Bleeding is still a major cause of morbidity and mortality in obstetrics. As recent reports have documented the successful treatment of some cases of postpartum hemorrhage (PPH) refractory to standard treatment with recombinant activated factor VII (rFVIIa), we have performed a systematic review of the existing literature on this topic. Although supported by few and uncontrolled studies, on the whole the published data suggest a potential role of rFVIIa in the management of severe PPH. However, further evidences are needed in order to better assess the optimal dose, the effectiveness and the safety of rFVIIa in such critical bleeding condition.

INTRODUCTION

Postpartum hemorrhage (PPH) is one of the most important causes of massive obstetrical hemorrhage, and the leading cause of maternal mortality worldwide.^{1,2} For example, the direct pregnancy-related maternal mortality rate in the United States is approximately 7–10 women per 100,000 live births and national statistics suggest that approximately 8% of these deaths are caused by PPH.³ In industrialized countries, PPH usually ranks in the top three causes of maternal mortality, along with thromboembolism and hypertension. In the developing world, several countries have maternal mor-

tality rates in excess of 1000 women per 100,000 live births, and WHO statistics suggest that over 20% of maternal deaths are due to PPH, accounting for more than 60,000 maternal deaths per year.¹

PPH is traditionally defined as a blood loss greater than 500 mL after a vaginal delivery, or more than 1000 mL following cesarean delivery.⁴ However, because the estimate of blood loss at the time of birth tends to be inaccurate, other investigators have more recently proposed alternative definitions of PPH including the drop of hematocrit with respect of pre-delivery values⁵ or the amount of blood loss and transfusion requirement during time.^{6,7}

The leading cause of PPH is uterine atony, which accounts for at least 50% of all cases.⁸ Other risk factors include placental abnormalities (i.e. placenta previa, placenta accrete, placenta percreta), retained placental fragments, lower genital tract lacerations, uterine rupture and acquired [hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, disseminated intravascular coagulation (DIC), acquired hemophilia] or congenital (von Willebrand disease, factor XI deficiency, factor VII deficiency, Glanzmann thrombasthenia) coagulation disorders.⁹⁻¹⁵ The treatment of life-threatening PPH still remains challenging. The first-line standard treatments include medical measures such as replacement transfusion therapy and uterotonic drugs. However, in the cases of failure of conservative measures, the therapeutic alternatives include bilateral ligation of hypogastric arteries or of the arteries of the uterus, B-Lynch suture (a compression suture that runs through the full thickness of both uterine walls) and selective pelvic arterial embolization. In refractory cases it can be necessary to perform obstetric hysterectomy.¹⁶⁻¹⁹

In recent years new therapeutic measures to control the bleeding have gained attention. In particular, there is an increasing number of case reports where empirical '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,²⁰ has been useful in the treatment of massive PPH refractory to conventional medical and surgical therapy.^{14,21}

The current knowledge on the use of rFVIIa in PPH will be analyzed in this review.

LITERATURE SEARCH

We firstly performed an electronic search on PPH and rFVIIa on MEDLINE, EMBASE, SCOPUS, OVID and the Cochrane Library without temporal limits using different combinations of the following keywords: 'postpartum hemorrhage', 'PPH', 'bleeding', 'recombinant activated factor VII', 'rFVIIa'. In addition, the bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. Unpublished works were identified by searching the abstract books of the most important conferences on obstetric and hematological diseases. A total of 31 articles were retrieved from the literature search.²²⁻⁵²

THE ROLE OF rFVIIa IN PPH

Table 1 analyzes in detail the studies. Our analysis of the published data identified 31 articles/abstracts including 97 patients with PPH receiving rFVIIa.²²⁻⁵² In those reports cesarean section is associated with an increased risk of onset of PPH as, among the 85 deliveries reported, 32 (37.6%) were by vaginal route and 53 (62.4%) by cesarean section. As expected, uterine atony was the leading cause of PPH (23 cases, 27.8%), followed by vaginal or uterine lacerations (14 cases, 19.4%), placenta abnormalities (10 cases, 13.9%) and HELLP syndrome (8 cases, 11.1%). However, the fact that in 27% of the cases a concomitant acquired or congenital coagulopathy was present underlines the importance of the evaluation of bleeding history in pregnancy.

The first case report of successful treatment of intractable obstetric hemorrhage in a non-hemophilic patient using rFVIIa was published by Moscardo and colleagues,²² who reported that rFVIIa successfully controlled life-threatening PPH after caesarean section in a woman who developed severe DIC, liver dysfunction and renal failure. Breborowicz and colleagues²⁵ reported eight cases of peripartum hemorrhage treated with rFVIIa. Seven women underwent caesarean section for different indications and one woman delivered vaginally. In five cases rFVIIa was administered only after emergency hysterectomy, while in the remaining two cases the drug was effective in avoiding the need for hysterectomy. In all but one case, a single relatively low dose of rFVIIa (range 16.7-48 µg/kg) was effective in controlling bleeding. Segal and colleagues³⁵ managed 10 women with PPH over 3 years after conventional blood product repletion was unsuccessful. rFVIIa at doses of 60-100 µg/kg was administered and bleeding was stopped in four patients and reduced or controlled in three. Tanchev and colleagues⁴³ reported four cases of severe bleeding associated with uterine atony in the post-placental period successfully treated in all cases with rFVIIa. Mayo and colleagues⁴⁰ reported a series of 11 patients, managed according to a protocol of coagulopathy scoring, including three PPH cases. One patient with uterine atony did not respond whereas in the other two patients the blood loss decreased following rFVIIa administration. Ahonen and Jokela⁴¹ presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions and found a good response in 11 of them. In five of the 12 cases,

Table 1. Summary of the 31 studies reporting the use of rFVIIa in PPH

Authors ^{Reference}	Year	Pts	Age* (years)	Concomitant disease	Type of delivery	Hysterectomy	Initial dose of rFVIIa (µg/kg)*	Number of doses*	Response ^{†‡}
Moscardo <i>et al.</i> ²²	2001	1	33	1 At	1 CS	1	90	9	1
Brueckner <i>et al.</i> ²³	2001	1	31	1 At	1 CS	1	NR	NR	1 [§]
Mazzuccconi <i>et al.</i> ²⁴	2001	2	27.5 (22–34)	2 PPAH	2 VD	NR	90	8	2/2 (100)
Breborowicz <i>et al.</i> ²⁵	2002	8	33.9 (26–44)	4 At; 3 DIC; 1 AC	7 CS, 1 VD	5/8 (62.5)	24.5 (16.7–48)	1	7/8 (87.5)
Zupanic <i>et al.</i> ²⁶	2002	1	31	1 DIC-HELLP	1 CS	0	90	1	1
Sobieszcyk <i>et al.</i> ²⁷	2002	1	29	1 IOP	1 CS	1	NR	NR	1
Sokolic <i>et al.</i> ²⁸	2002	1	31	1 DIC-HELLP	1 CS	0	90	1	1
Baudo <i>et al.</i> ²⁹	2002	2	NR	2 PPAH	NR	NR	90	NR	2/2 (100)
Bouwmeester <i>et al.</i> ³⁰	2003	1	30	1 At-Lac	1 VD	1	60	2	1
Kretzschmar <i>et al.</i> ³¹	2003	1	35	1 DIC-AFE	1 CS	1	60	1	1 [§]
Boyer-Neumann <i>et al.</i> ³²	2003	1	29	1 VWD	1 CS	0	41	5	1
Dart <i>et al.</i> ³³	2004	1	24	1 HELLP	1 VD	0	90	1	1
Boehlen <i>et al.</i> ³⁴	2004	1	31	1 At	1 VD	1	120	19	1
Segal <i>et al.</i> ³⁵	2004	10	NR	3 PA; 2 At; 4 Lac; 1 UM	NR	7/10 (70.0)	88.0 (60–100)	1.1 (1–2)	10/10 (100)
Merchant <i>et al.</i> ³⁶	2004	3	30	3 HELLP	3 CS	0/3	90	2	3/3 [†]
Lim <i>et al.</i> ³⁷	2004	1	26	1 DIC-AFE	1 VD	0	90	1	1
Price <i>et al.</i> ³⁸	2004	1	32	1 HELLP	1 CS	0	90	1	1
Gidiri <i>et al.</i> ³⁹	2004	1	38	1 PA	1 CS	0	170	1	1
Mayo <i>et al.</i> ⁴⁰	2004	3	30.0 (27–34)	1 At; 1 IOP; 1 RDF	1 CS, 2 VD	2/3 (66.7)	NR	NR	2/3 (66.7)
Ahonen and Jokela ⁴¹	2005	12	27.7 (24–37)	3 PA; 2 At; 1 PP; 6 Lac	5 CS, 7 VD	5/12 (41.7)	85.1 (42–120)	1	10/12 (83.3)
Shamsi <i>et al.</i> ⁴²	2005	3	30.7 (27–35)	1 PP; 2 Lac	3 CS	2/3 (66.7)	86.7 (80–90)	1	3/3 (100)
Tanchev <i>et al.</i> ⁴³	2005	4	NR	4 At	4 VD	0/4	72.0 (61–82)	1	4/4 (100)

Table 1. Continued

Authors ^{Reference}	Year	Pts	Age* (years)	Concomitant disease	Type of delivery	Hysterectomy	Initial dose of rFVIIa (µg/kg)*	Number of doses*	Response**
Holub <i>et al.</i> ⁴⁴	2005	1	28	1 At	1 CS	1	NR	1	1
Hollnberger <i>et al.</i> ⁴⁵	2005	3	29.7 (28–31)	2 At, 1 PP	1 CS, 2 VD	0/3	100.0 (60–120)	2	3/3
Nowacka <i>et al.</i> ⁴⁶	2005	1	30	1 IOP	1 CS	1	37.5	2	1
Verre <i>et al.</i> ⁴⁷	2006	1	24	1 At	1 CS	1	90	1	1
Palomino <i>et al.</i> ⁴⁸	2006	3	NR	1 At, 1 PP, 1 AP	2 CS, 1 VD	1/3 (33.3)	40	1	3/3 (100) [†]
Heilmann <i>et al.</i> ⁴⁹	2006	1	29	1 At	1 CS	0	90	1	1
Pepas <i>et al.</i> ⁵⁰	2006	1	NR	1 HELLP-DIC	1 CS	0	105.0 (90–120)	2	1
Kulkarni <i>et al.</i> ⁵¹	2006	1	30	1 FVII	1 CS	0	NR	NR	1
Sobieszczyk <i>et al.</i> ⁵²	2006	25	30 (23–44)	2 UM, 1 AC, 8 DIC	16 CS, 9 VD	13/25	32.2 (10–137)	1.2 (1–2)	24/25 (96.0)
Total		97	30.5 (22–44)		53 CS, 32 VD	44/93 (47.3)	53.1 (10–170)	1.5 (1–19)	92/97 (94.8)

*Absolute number or median (range).

†Number (percentage).

‡Defined as cessation or significant reduction of bleeding.

§rFVIIa had reduced bleeding but one patient died due to multi-organ failure.

¶A patient died of cardiac arrest.

AC, anticoagulation; AFE, amniotic fluid embolism; AP, abruptio placentae; At, atony; CS, cesarean section; DIC, disseminated intravascular coagulation; FVII, congenital factor VII deficiency; HELLP, hemolysis, elevated liver enzymes and low platelets; IOP, intraoperative bleeding; Lac, uterine, vaginal or other lacerations; NR, not reported; PA, placenta accreta; PP, placenta praecura; PPAH, postpartum acquired hemophilia; PPH, postpartum hemorrhage; Pts, patients; RDE, retained dead fetus; rFVIIa, activated recombinant factor VII; UM, uterus myomatosus; VD, vaginal delivery; VWD, von Willebrand disease.

hysterectomy was performed before the administration of rFVIIa. However, as rFVIIa was effective in avoiding hysterectomy in most of the remaining patients, the authors concluded that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery. In the largest case series published recently by Sobieszcyk and colleagues⁵² who collected 25 PPH cases from an international internet-based registry, rFVIIa stopped or decreased obstetrical bleeding in all but one patient.

As regards the use of rFVIIa in obstetrical patients with underlying congenital coagulopathies, Boyer-Neumann and colleagues³² reported the successful management of post-cesarean uterine bleeding using the sequential combination of recombinant FVIII and rFVIIa in an alloimmunized patient with type 3 von Willebrand disease. Kulkarni and colleagues⁵¹ described 14 pregnancies in seven women with inherited FVII deficiency. In one case, rFVIIa was successfully used to manage a PPH case. Similarly, there are other few cases reported in literature on the use of rFVIIa in postpartum acquired hemophilia A.^{24,29} Mazzucconi and colleagues²⁴ described four postpartum inhibitor cases treated with high-dose immunoglobulin and dexamethasone; in two women bleeding symptoms were stopped by the concomitant use of rFVIIa at a dose of 90 µg/kg every 1 hour for 4 days. Other cases successfully treated with rFVIIa have been collected by Baudo and de Cataldo in the Register of acquired factor VIII inhibitors (RIIA) from the Italian Association of Hemophilia Centres (AICE).²⁹

Nearly half of the cases where information on the mode of delivery was available (44/93) underwent hysterectomy; however, the impact of rFVIIa on avoiding the need for emergency hysterectomy and preservation of reproductive function is difficult to determine as in many cases this surgical procedure was performed before drug usage. In the majority of cases (67.7%), bleeding was reduced after a single dose of rFVIIa, although in some cases an additional dose was required to achieve hemostatic efficacy. The mean dose of rFVIIa administered was 53.1 µg/kg, which is less than that usually recommended for hemophiliacs with inhibitors (90 µg/kg). Thus, some experts¹⁸ suggest in this clinical setting a dose of rFVIIa of 40–60 µg/kg which may be repeated if there is a lack of clinical improvement within 15–30 minutes from the administration of the drug.

As regards the assessment of the effectiveness of rFVIIa, the majority of the authors defined a positive

result when rFVIIa led to cessation or significant reduction in either blood loss or need for blood transfusion. Using this definition, among the 97 reported cases, a positive result was obtained in all but five cases (94.8% of efficacy). However, we advise particular caution in interpreting this result as all data available in literature were derived from uncontrolled studies including single cases or small series of patients. Thus, the true effectiveness of rFVIIa in these bleeding situations could be overestimated, those cases with a positive outcome being reported preferentially.

Another open issue regards the safety of rFVIIa in life-threatening PPH, particularly considering that in a number of cases a concomitant systemic activation of the coagulation (i.e. DIC) may exist. Although no drug-related adverse reactions, especially thrombotic episodes, have been reported so far in this specific subgroup of patients, we advise physicians to follow experts' recommendations^{18,53} as regards the dose and timing of rFVIIa administration and to monitor closely such patients not only for their clinical bleeding condition but also for the onset of thrombotic complications.

In summary, based on the existing literature, many experts recommend the use of rFVIIa as an adjunctive therapy in the management of severe and/or life-threatening PPH.¹⁴ However, it is important to avoid using rFVIIa as a 'last resort' and only after everything else fails. In fact, patients with PPH at this stage are so metabolically compromised that no therapy can reverse their decline and rFVIIa might be of no value.⁵⁴ A relatively early intervention to control PPH appears to be crucial for the success of rFVIIa. Nevertheless, as recently stated by Vincent and colleagues,⁵³ rFVIIa should not be considered as a substitute for, nor should it delay, the performance of life-saving procedure such as embolization or surgery.

CONCLUSIONS

Although limited, the published data suggest that rFVIIa could be an important addition to the hemostatic strategies available for the control of bleeding in patients with life-threatening PPH.

However, further studies are greatly encouraged in order to validate the efficacy of rFVIIa to control intractable obstetrical bleeding and better assess its optimal dose, timing of administration and safety profile.

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