Journal of Thrombosis and Haemostasis, **13**: 520–529 DOI: 10.1111/jth.12844

ORIGINAL ARTICLE

Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial

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To cite this article: Lavigne-Lissalde G, Aya AG, Mercier FJ, Roger-Christoph S, Chauleur C, Morau E, Ducloy-Bouthors AS, Mignon A, Raucoules M, Bongain A, Boehlen F, de Moerloose P, Bouvet S, Fabbro-Peray P, Gris JC. Recombinant human FVIIa for reducing the need of invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. *J Thromb Haemost* 2015; **13**: 520–9.

Summary. *Background:* Case reports on recombinant human factor VIIa (rhuFVIIa) use in women with severe postpartum hemorrhage (PPH) showed encouraging results, but no randomized controlled trial (RCT) is available. *Patients and methods:* Eighty-four women with severe PPH unresponsive to uterotonics were randomized to receive one early single rhuFVIIa infusion ($n = 42$) or standard care (no rhuFVIIa; $n = 42$). The primary efficacy outcome measure was the reduction of the need for specific second-line therapies, such as interventional hemostatic procedures, for blood loss and transfusions. The primary safety outcome measure was the number of deaths and thrombotic events during the 5 days following rhuFVIIa infusion. *Results:* rhuFVIIa was associated with a reduction in the number of patients who needed second-line therapies compared with controls (standard care). Specifically, 39/42 (93%) patients in the standard care arm received second-line therapies and 22/42 (52%) patients in the rhuFVIIa arm (absolute difference, 41%; range, 18–63%; relative risk RR, 0.56 [0.42–0.76]). The delivery mode (vaginal or Cesarean section) did not affect the primary outcome. No death occurred. Two venous thrombotic events were recorded in the rhuFVIIa arm: one ovarian vein thrombosis and one deep vein thrombosis with a non-severe pulmonary embolism. *Conclusion:* This open RCT in women with severe PPH refractory to uterotonics shows that rhuFVIIa reduces the need for specific second-line therapies in about one in three patients, with the occurrence of non-fatal venous thrombotic events in one in 20 patients.

Keywords: FVIIa activated; hysterectomy; postpartum hemorrhage; treatment efficacy; treatment outcome.

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Received 3 February 2014
Manuscript handled by: F. R. Rosendaal
Final decision: F. R. Rosendaal, 31 December 2014

Introduction

Obstetric hemorrhages, mainly postpartum hemorrhages (PPH), are the most common cause of maternal mortality worldwide. They remain a problem even in developed countries. Indeed, in France, hemorrhages are still responsible for about 2.5 maternal deaths per 100 000 births per year [1–4]. The incidence of severe maternal morbidity due to PPH has been estimated to be 4.5–6.7 per 1000 deliveries in the United Kingdom [5]. The clinical consequences comprise severe anemia, hemorrhagic

1. **The delivery mode(vaginal or Cesarean section) did not affect the primary outcome.**
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2. **rhuFVIIa was associated with a reduction in the number of patients who needed second-line therapi...**
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shock, organ failures including acquired coagulation disorders, venous thromboembolic disease (VTE) and peripartum hysterectomy [6,7].

Primary PPH is defined as blood loss from the genital tract in excess of 500 mL following vaginal delivery or in excess of 1000 mL following Cesarean birth, within the first 24 h of delivery. Reports in developed countries suggest that about 1% of deliveries are associated with severe PPH [8–11]. This type of hemorrhage is responsible for one out of four [3] deaths among the estimated number of 500 000 women who die as a consequence of pregnancy each year [12]. Approximately 70% of primary PPH are due to uterine atony [13].

International agencies recommend the early administration of uterotonic agents (i.e. sulprostone) as first-line therapy, associated with fluid supply, controlled cord traction and uterine massage after placenta delivery, empty bladder catheterization and bimanual uterine compression [14–16]. Thereafter, specific second-line therapies include uterine compression sutures (B-Lynch surgical techniques or its various modifications), ligation of the uterine or internal iliac arteries, uterine artery embolization and peripartum hysterectomy.

Recombinant human activated factor VII (rhuFVIIa; Novoseven®, Novonordisk A/S, Baagsvaerd, Denmark) activates coagulation to generate a thrombin burst and stabilize blood clots. Off-label use of rhuFVIIa for massive PPH has been prompted by clinical case series describing the efficacy of high-dose rhuFVIIa in this setting [17]. After the formal beginning of this randomized controlled trial (RCT), Welsh *et al.* and Phillips *et al.* published, based on their experience and on the published cases series, guidelines and an algorithm for the use of rhuFVIIa at 90 μg kg^{-1} in patients with PPH after surgical intervention (arterial embolization, arterial ligatures and peripartum hysterectomy) [18,19]. A recent systematic review of 272 patients suggested that rhuFVIIa might be useful for the management of severe refractory PPH compared with standard treatment [20,21].

The aim of this RCT was to assess the efficacy and safety of a single rhuFVIIa infusion given to women with severe PPH after sulprostone failure.

Methods

This multicenter, randomized, open, controlled trial involving two parallel arms with an allocation ratio of 1 : 1 was conducted between February 2007 and November 2010 at eight University hospitals in two countries. Written informed consent was obtained from each patient or the legally acceptable surrogate when the patient was unable to give consent. The consent procedure was in accordance with national laws on clinical research: Article L.1121-5; Article L.1121-8; Article L.1122-1-2, (http://www.legifrance.gouv.fr).

The trial was registered at http://clinicaltrials.gov/NCT00370877. This RCT is reported in accordance with the CONSORT statement 2010 [22,23].

Patients

The inclusion criteria were: patients aged 18 years or older who delivered their babies after the end of the 27th week of amenorrhea and who developed severe primary PPH after vaginal delivery or Cesarean section that persisted after sulprostone treatment.

The non-inclusion criteria were: age < 18 years, personal history of thrombotic events and not-approved written informed consent.

Severe primary PPH was defined as the loss of more than 1500 mL of blood within 24 h after birth. The contribution of any fluid used for washing was taken into account to prevent blood loss overestimation.

According to French practice guidelines [14] first-line therapies for PPH included: fluid resuscitation, bladder catheterization, manual removal of retained placenta, genital tract examination, uterine exploration, oxytocin (20–30 IU every 10–30 min) and finally one sulprostone infusion (500 μg within 1 h).

Treatment evaluation

The enrolment criterion was sulprostone failure 1 h after the infusion onset (or before the end of this period). At each site, enrolled patients were then randomly assigned to two groups: one group received one early single intravenous dose of 60 μg kg^{-1} rhuFVIIa (intervention arm) and the other group did not (standard care arm) (Fig. 1). This rhuFVIIa dose was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with this drug.

Block randomization stratified by center was used with balanced blocks of six patients with a 1 : 1 allocation ratio that was implemented at each center. The randomization list was computer generated (using the SAS software 9.3, SAS Institute Inc, Cary, NJ, USA) centrally by PFP, who was not involved in the patients' management.

To facilitate the emergency treatment with complete Novoseven® packaging units (1.2, 2.4 and 4.8 mg vials), the theoretical rhuFVIIa dose was tabulated and adapted as described in Table 1. 'Under-treated' and 'over-treated' patients were women who received a total rhuFVIIa dose above or below, respectively, the recommended dose.

At each center, the management of patients in both arms complied with the local care guidelines for severe PPH.

For compassionate reasons, patients assigned to the standard care arm and with very severe PPH received late rhuFVIIa treatment at similar doses in an attempt to avoid emergency peripartum hysterectomy.

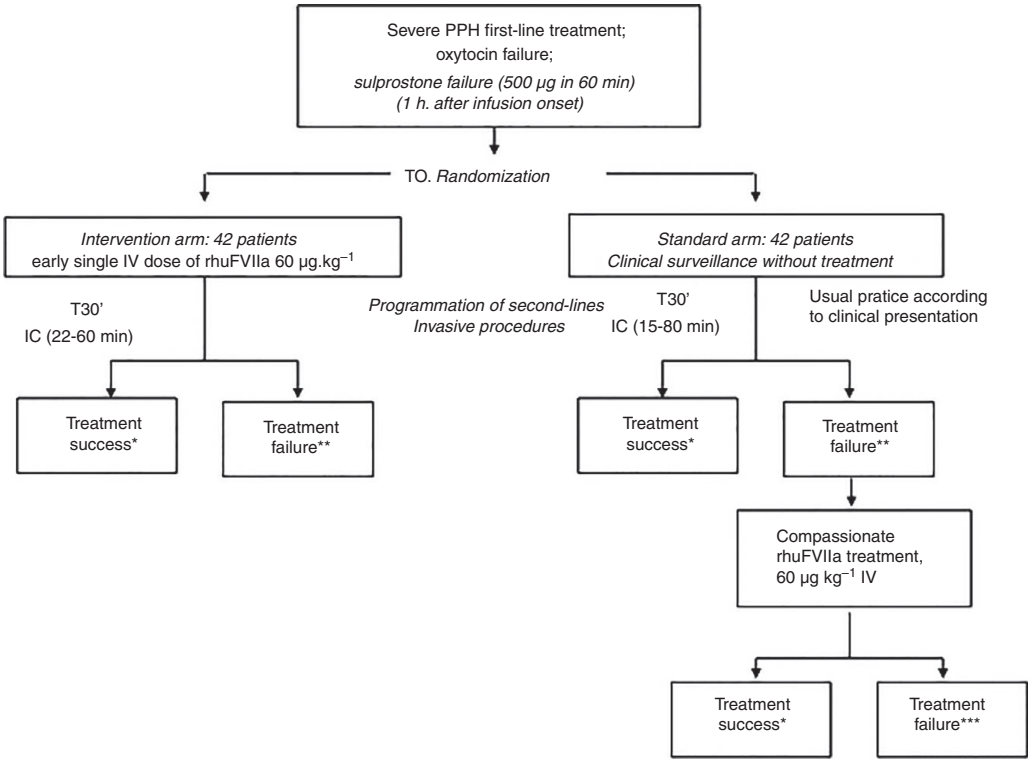

Fig. 1. Trial design. *No need for specific second-line therapy (primary outcome). **Need for specific second-line therapies (compression sutures and/or uterine artery embolization and/or vascular ligations and/or hysterectomy) depending on availability (primary outcome). ***Hysterectomy.

Table 1 Recommended rhuVIIa dosage in the RCT

Body weight (kg)*	Recommended dosage (mg) (~60 µg kg^{-1})
40–45	2.4
46–68	3.6
69–94	4.8
95–110	6
> 110	6

*The theoretical rhuFVIIa dose was 60 µg kg−1 (based on the patient's weight at term minus 5 or 7 kg in the case of twin pregnancy, as an approximation of the fetal-placental weight).

Replacement therapy

Packed red blood cells (PRBCs) were indicated if the patient's hemoglobin concentration was lower than 8 g dL^{-1}. Platelet concentrates (PC) were administered when the platelet count was lower than 50×10^9 L^{-1} (http://www.has.sante.fr/hemorragies-du-post-partum-immediat). Fibrinogen concentrates were administered if the plasma fibrinogen concentration was lower than 1 g L^{-1}. Hemostatic drugs are not recommended and not routinely used as first-line intervention in PPH: therefore, they were not recommended in our RCT. The use of tranexamic acid (TXA) (0.5–1 g intravenously) was left to the attending physician's discretion.

Vascular volume expansion was achieved using 500 mL of crystalloid and 500 mL of colloid expander for the first liter of blood loss, and thereafter an infusion, mostly of gelatin, was administered to compensate for the subsequent blood loss (vol/vol). Fresh frozen plasma (FFP) was infused by the attending anesthetist, if clinically indicated.

Efficacy assessment

Treatment success was defined as the absence of need for specific second-line therapies. Classically, interventional hemostatic procedures include uterine compression sutures (B-Lynch surgical technique or its various modifications), ligation of the uterine or iliac arteries, uterine artery embolization and peripartum hysterectomy [14] and the Bakri Balloon, which was used once in this study. During the study period (2007–2010), uterine compression sutures alone (without vascular ligation) were also used (n = 3). Although this procedure was not speci-

1. **ommended in our RCT. The use of tranexamic acid(TXA)(0.5–1 g intravenously) was left to the attendi...**
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fied in the initial study protocol, we included it in the primary composite outcome to avoid any overestimation of the treatment effect.

Blood loss had to be measured using a plastic collector bag. Any transfusions of packed red blood cells (PRBCs), platelet concentrates (PC) and fresh frozen plasma units (FFP) were analyzed.

Bleeding was considered to have stopped (i.e., treatment success) if the estimated blood flow decreased to less than 50 mL per 10 min within the 30 min following randomization.

At any time and in both arms, invasive second-line treatments were considered if bleeding was uncontrolled (blood flow higher than 50 mL per 10 min) or intractable (defined as PPH > 2500 mL, or blood flow > 500 mL per 30 min, or hemorrhagic shock refractory to standard care).

Safety assessments

We recorded the relevant adverse events (AE) and serious adverse events (SAE) that occurred within 5 days after the PPH end. AE included symptomatic thrombotic manifestations (myocardial infarction, ischemic stroke, deep-vein thrombosis [DVT] and pulmonary embolism [PE]) and death. SAE were defined as any AE that contributed to the occurrence of death, or that could have jeopardized the immediate prognosis, or that caused incapacity or prolonged hospitalization. Thromboprophylaxis was at the attending physician's discretion. The primary safety outcome was the occurrence of any objectively proven symptomatic thrombotic manifestation or death.

Data collection

Each participating center collected data up to 5 days after the PPH ended. The patient-related data collected included: age and weight at term, anesthesia and delivery mode (spontaneous vaginal or elective or non-elective Cesarean delivery). PPH risk factors were also collected (Table 2). The hemodynamic status (systolic blood pressure [mm/Hg], diastolic blood pressure [mm/Hg] and heart rate [bpm]) was also recorded.

The primary outcome measures were: interventional second-line treatments, defined as radiological interventional procedures (uterine or internal iliac artery embolization), surgical ligation of the uterine or internal iliac arteries and any uterine devascularization technique, conservative surgical approaches (B-lynch sutures, Bakri Balloon and variants with hemostatic intention) or peripartum hysterectomy.

The secondary outcome measures were: number (percentage) of patients in each arm who received PRBCs, FFP units or PC; all replacement treatments (infusion of colloids/crystalloids, transfusions of blood components such as PRBCs, FFP and PC, and additional procoagulant treatments such as TXA, fibrinogen concentrates and aprotinin) were recorded.

Biological measures were collected before delivery and within the first 12 h after PPH (Table S1).

The initial observation period was 5 days due to the limited Novoseven® biological half-life (4–6 h). To identify symptomatic venous thromboembolism events up to 6 weeks after PPH, data from the initial medical records were extracted and patients had to fill in a simple questionnaire concerning the first 6 weeks postpartum.

Statistical analysis

Calculation of the sample size required To detect an absolute reduction of 30% in the need for specific second-line therapies (uterine compression sutures, uterine artery embolization, vascular ligation or peripartum hysterectomy), from 70% in the standard care arm (standard of care recommendations from the French Haute Autorité de Santé: http://www.has-sante.fr/portail/jcms/c_272417/hemorragies-du-post-partum-immediat) to 40% in the intervention arm with a two-sided test and a type one error of 5% and a power of 80%, 42 patients were required in each group. We chose to focus on an absolute reduction of only 30% based on our limited inclusion capacities.

Analysis Quantitative data are reported as medians with lower quartile (Q25%) and upper quartile (Q75%) values. Qualitative variables are reported as numbers and percentages. All analyses were performed based on the intention-to-treat (ITT) principle.

We compared the primary and secondary outcomes between arms by estimating the relative risk (RR) using the Mantel-Haenszel method, with a 95% confidence interval (95% CI), providing a *P*-value from the associated Mantel-Haenszel chi-square test. The existence of treatment by center interactions for the primary outcome was assessed using the Breslow-Day test, first applied to the eight centers and then only to the five centers that enrolled at least five patients. Among all the presented analyses, only the treatment by center interaction and the effect of the delivery mode on the primary outcome were '*post hoc*' analyses. All tests were two sided and assessed at the 5% significance level.

Results

Baseline characteristics

A total of 84 parturient women with severe PPH were enrolled (Fig. 2). Sixty patients were included 1 h after sulprostone infusion. Among the 24 remaining patients, the median randomization time (lower quartile–upper quartile) was 40 min (30–45 min) for the intervention arm and 30 min (30–30 min) for the standard care arm

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Table 2 Baseline characteristics of the study population

	Total $N = 84$	Standard care arm $n = 42$	Intervention arm $n = 42$
Demographic characteristics			
Maternal age (years), median [Q25–Q75%]	31 [28–37]	30 [28–35]	32 [27–37]
Pre-delivery weight (without the weight of the baby), median [Q25–Q75%], kg	69 [61–78]	70 [60–79]	68 [62–76]
Pregnancy data			
Gravidity, median [Q25–Q75%]	3 [2–4]	3 [2–4]	3 [2–3]
Parity, median [Q25–Q75%]	2 [1–3]	2 [2–3]	2 [1–3]
Nulliparous, n [%]	23 [27]	8 [19]	15 [36]
Twin pregnancy, n [%]	14 [17]	7 [17]	7 [17]
Mode of delivery, n [%]			
Cesarean section delivery	43 [51]	20 [48]	23 [55]
Vaginal delivery	41 [49]	22 [52]	19 [45]
Mode of anesthesia, n [%]			
Neuraxial anesthesia	69 [82]	34 [81]	35 [83]
General anesthesia	15 [18]	8 [19]	7 [17]
Cause of primary postpartum hemorrhage, n [%]			
Uterine atony	75 [89]	36 [85]	39 [93]
Placenta retention	5 [6]	1 [2]	4 [10]
Genital tract injury	4 [5]	1 [2]	3 [7]
Abnormal placental insertion	14 [17]	8 [19]	6 [14]
Other	5 [6]	1 [2]	4 [10]
One cause	70 [83]	38 [91]	32 [76]
Multiple causes	14 [17]	4 [10]	10 [24]
Main hemostasis-related biological indicators at inclusion (T0)			
	$N = 73$	$N = 38$	$N = 35$
Fibrinogen plasma level (g L^{-1}), median [Q25–Q75%]	2.9 [2.3–3.6]	3.2 [2.3–3.6]	2.4 [2–3.8]
	$N = 80$	$N = 41$	$N = 39$
Platelet count (g L^{-1}), median [Q25–Q75%]	140 [110–205]	145 [115–208]	136 [103–197]
	$N = 80$	$N = 41$	$N = 39$
Hemoglobin (g dL^{-1}), median [Q25–Q75%]	9.3 [7.8–10.4]	9.5 [8.6–10.4]	8.5 [6.5–10.2]

($P = 0.93$). The patients' baseline characteristics are presented in Table 2.

Primary outcomes

The primary efficacy outcomes are detailed in Table 3. Interventional hemostatic procedures (i.e. the composite primary efficacy outcome) were required for 93% ($n = 39/42$) of patients in the standard care arm and for 52% ($n = 22/42$) of patients in the intervention arm ($P < 0.0001$; RR = 0.56; 95% CI, 0.42–0.76). The mean number of patients who needed to be treated with rhuFVIIa (number needed to treat, NNT) to avoid one composite outcome was 2.6. Only the number of arterial embolization procedures was significantly lower in the intervention arm than in the standard care arm. The percentage of peripartum hysterectomies was 7% ($n = 3$) in the intervention arm and 19% ($n = 8$) in the standard care arm (RR = 0.375 (0.107–1.32); $P = 0.11$).

No effect of treatment by center interaction on the primary efficacy outcome was detected. Indeed, the RR value adjusted for the eight centers was 0.7 with 95% CI 0.55–0.9 (Breslow-Day test, $P = 0.06$). The result did not change even when only the five centers that enrolled at least five patients were included in the analysis (RR = 0.71; 95% CI, 0.55–0.91; Breslow-Day test, $P = 0.3$).

The time to initiation of a second-line treatment was not different between groups: the median delay was 30 min (95% CI, 15–80 min) for the 39 patients in the standard care arm and also 30 min (95% CI, 22 min: 60 min; $P = 0.93$) for the 22 patients in the intervention arm who did not respond to rhuFVIIa.

In deviation from the trial protocol, blood loss-failed to be measured. The use of a plastic collector bag to quantify postpartum blood loss was encouraged; the devices were provided to the different healthcare teams, but were only marginally used, thus rendering the systematic measurement of blood loss volumes impossible.

To determine the proportion of patients in the two arms who required blood products, the transfusion needs were assessed before and after randomization. Before randomization, the absolute numbers of transfused PRBCs and

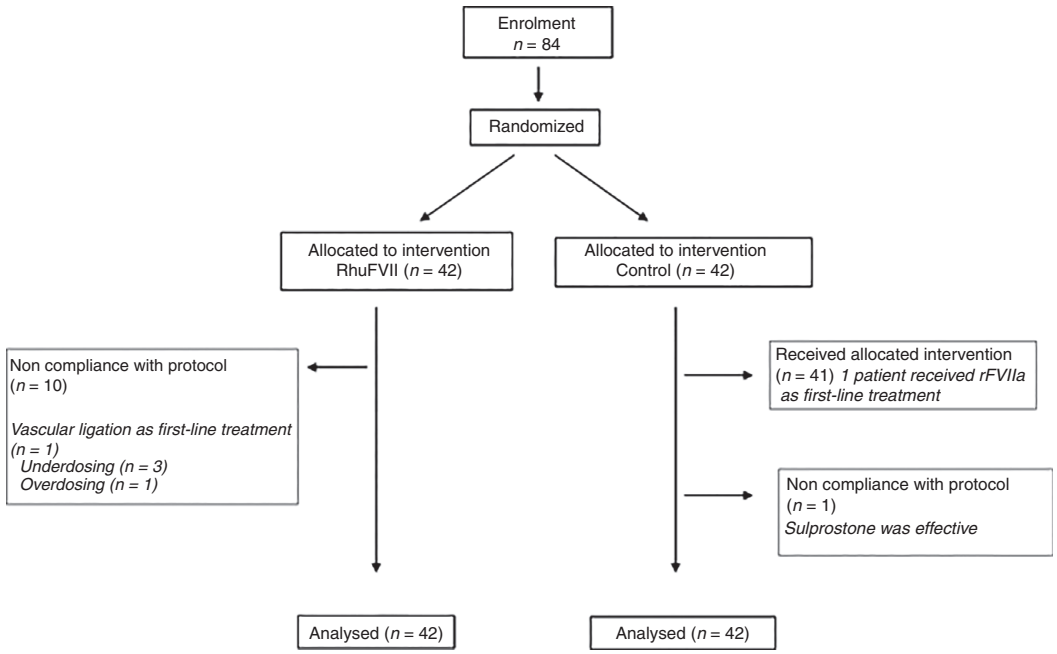

Fig. 2. Flow chart of inclusions.

Table 3 Efficacy outcomes

Outcomes	Standard arm (N = 42) n (%)	Intervention arm (N = 42) n (%)	Absolute difference [95% CI]	Relative risk [95% CI]	Mean NNT	P
Primary efficacy outcome	39 (93)	22 (52)	41% [18; 63]	0.56 [0.42; 0.76]	2.6	< 0.0001
Arterial embolization	24 (57)	12 (29)	28% [−4; 61]	0.5 [0.29; 0.86]	3.5	0.0082
Arterial ligation	12 (29)	9 (21)	8% [−30; 44]	0.75 [0.35; 1.59]	14	0.45
Peripartum hysterectomy	8 (19)	3 (7)	12% [−28; 52]	0.38 [0.11; 1.32]	8.4	0.11
Others*	6 (14)	4 (10)	4% [−36; 44]	0.67 [0.20; 2.19]	25	0.50
B-lynch sutures, Bakri Balloon and variants with hemostatic intention						

FFP were (median value [Q25–Q75%] values): 0 [0–1] vs. 0 [0–2] in the standard care arm and 0 [0–0] vs. 0 [0–0] in the intervention group. The percentages of patients who required PRBCs, FFP and PC were 26% vs. 38% (P = 0.24), 14% vs. 14% and 4.8% vs. 2.4% in the standard care and in the intervention arm, respectively. After randomization, the absolute numbers of transfused PRBCs and FFPs were (median value [Q25–Q75%] values): 2 [0–4] vs. 2 [0–3] and 0 [0–4] vs. 0 [0–3] in the standard care and intervention arm, respectively. The percentages of women requiring PRBCs, FFP and PC were 67% vs. 60%, 48% vs. 45% and 31% vs. 26%, respectively. No between-group difference was thus observed in the absolute numbers of administered blood products.

Safety outcomes Two venous thrombotic events were reported, both in the intervention arm (2/42, 5%; 95% CI upper limit, 11% vs. 0/42; P-value, 0.25). One woman pregnant with twins had severe PPH following delivery by Cesarean section ('appropriately treated' patient; total rhuFVIIa dose, 54.6 μg kg^{-1}). Two days after the rhuFVIIa infusion, she had a short segmental thrombosis of the right ovarian vein, discovered on a CT scan prescribed for intestinal occlusion in a non-infectious context. Recovery was uneventful after anticoagulant treatment with enoxaparin. The second patient developed DVT of the lower limb associated with moderate PE 5 days after delivery by Cesarean section due to placental abruption and intrauterine fetal death ('under-treated' patient; total rhuFVIIa dose,

31.6 μg kg^{-1}). PPH was due to uterine atony and required blood transfusion. Late thrombotic complications occurred, despite the thromboprophylaxis initiated 6 h after the end of PPH (4000 IU enoxaparin, once a day). Recovery was uneventful after adapted treatment. No maternal death occurred during the trial. No additional thrombotic event and no serious adverse event were reported during the first 6 weeks postpartum.

Secondary outcomes

Analysis of the replacement treatments used in the two arms showed that at T0, 33% (6/18) of the evaluable women in the standard care arm and 42% (10/24) of those in the intervention arm had received fibrinogen concentrates; the percentages were identical for TXA. Aprotinin was administered to one patient in each arm. After T0, 67% (10/24) of the evaluable patients in the standard care arm and 48% (10/21) of those in the intervention arm received fibrinogen concentrates; 47% (7/15) of women in the standard care arm and 44% (8/18) in the intervention arm received TXA. Aprotinin was administered to 14% (2/14) of women in the standard care arm and to 6% (1/16) of patients in the intervention arm.

The fall in hemoglobin concentration between T0 and T30 was significantly different between groups ($P = 0.0377$), with a median decrease of -0.2 g dL^{-1} (IQ = [−1, 1.8]) in the intervention arm and of -0.9 g dL^{-1} (IQ = [−2.3, 0.1]) in the standard care arm. The hemoglobin concentration fall was thereafter categorized as higher than 2 g dL^{-1} vs. all the other values. The highest hemoglobin falls (> 2 g dL^{-1}) were detected in 15% (5/33) of patients in the intervention group and in 30% (8/27) in the standard care arm ($P = 0.18$).

The primary efficacy outcome measures were not affected by the delivery mode (Table 4A,B) (absolute risk difference = 44% for vaginal delivery and 39% for Cesarean section). The significantly lower frequency of interventional hemostatic procedures in the intervention arm was confirmed also when these patients were classified based on the delivery mode (vaginal delivery, RR = 0.52, 95% CI, 0.32–0.81; Cesarean section, RR = 0.6, 95% CI, 0.41–0.86).

Relationship between rhuFVIIa dose and efficacy

The median rhuFVIIa dose infused into patients was 57.6 μg kg^{-1} (inter-quartile range, 52.9–60.8; range, 31.6–72.7 μg kg^{-1}).

The infused rhuFVIIa dose was based on the conversion of the theoretical weight-adjusted dose into discrete total doses corresponding to the use of a number of complete product vials (Table 1). Eight patients were categorized as 'under-treated' and one as 'over-treated'. The primary efficacy outcomes were not different between 'over-treated or appropriately treated' women ($n = 34$) and 'under-treated' women ($n = 8$) ($P = 0.45$, Fisher's exact test). The median value of the difference between theoretical rhuFVIIa dose and infused rhuFVIIa dose was -1.64 μg kg^{-1} for women who required some form of second-line intervention, and -3.2 μg kg^{-1} for successfully treated women who recovered without any second-line intervention ($P = 0.55$).

Table 4 Effect of the delivery mode on the efficacy outcomes. (A) Vaginal delivery. (B) Delivery by Cesarean section

Principal endpoint	Standard arm ($N = 42$) n (%)	Intervention arm ($N = 42$) n (%)	Absolute difference (%)
Vaginal delivery, $N = 41$	$N = 22$	$N = 19$	
A			
Primary efficacy outcome	20 (91)	9 (47)	44
Arterial embolization	16 (73)	7 (37)	36
Arterial ligation	2 (9)	2 (11)	−2
Peripartum hysterectomy	3 (14)	1 (5)	9
Others*	2 (9)	0	9
Arterial embolization alone	15 (68)	7 (37)	31
Arterial ligation alone	0 (0)	1 (5)	−5
Cesarean section delivery, $N = 43$	$N = 20$	$N = 23$	
B			
Primary efficacy outcome	19 (95)	13 (57)	38
Arterial embolization	8 (40)	5 (22)	18
Arterial ligation	10 (50)	7 (30)	20
Peripartum hysterectomy	5 (25)	2 (9)	16
Others*	4 (20)	4 (17)	3
Arterial embolization alone	7 (35)	5 (22)	13
Arterial ligation alone	3 (15)	3 (13)	2

*B-lynch sutures, Bakri Balloon and variants with hemostatic intention.

Compassionate treatment

In the standard care arm, salvage peripartum hysterectomy was considered after vascular embolization or ligation failure. Therefore, eight of the 42 patients received late rhuFVIIa as a compassionate treatment in an attempt to avoid surgery. Peripartum hysterectomy was avoided in two cases.

Discussion

This first multicenter RCT on the off-label use of rhuFVII in women with PHH shows that early infusion of one single rhuFVIIa dose after sulprostone failure can reduce the need for specific second-line interventions from 93% (in the standard care arm) to 52% (absolute difference of 41%). The NNT to avoid at least one second-line therapy was 2.6. This positive effect was independent from the delivery mode. The results also indicate that the intervention was not successful in over half the women.

In their review, Franchini *et al.* [18] recommended the administration of 90 μg kg^{-1} rhuFVIIa and in the case of PPH treatment failure to give a similar dose 20 min later. In a more recent Japanese multicenter case series of 25 women [21], the median number of rhuFVIIa infusions was one (range, one to five), the median dose per administration was 84.0 μg kg^{-1} (range, 21–105 μg kg^{-1}) and the median total dose was 97.9 μg kg^{-1} (range, 55.0–359 μg kg^{-1}). After the final administration, bleeding was 'stopped' in 16 patients (64%), 'decreased' in eight patients (32%) and 'unchanged' in one patient (4%). Peripartum hysterectomy was required in two patients (15.4%) after rhuFVIIa administration. In a recent larger case series of 110 women included in the Australian and New Zealand registry, 78% of patients received a single rhuFVIIa infusion (median dose, 92 μg kg^{-1}) [19], the clinically estimated positive response rate was 76%, and 64% of women responded to the first dose. As severe PPH is considered to be a thrombogenic event and rhuFVIIa is associated with thromboembolic complications in this clinical setting, we decided for safety reasons to use a single infusion at lower doses (between 60 and 90 μg kg^{-1}) than previously reported [24]. During the 5-day follow-up after delivery, one ovarian vein thrombosis and one DVT with PE were reported, but no arterial thromboembolic events.

In this RCT, 19% of women in the standard care arm underwent peripartum hysterectomy. A national cohort study in the United Kingdom between 2007 and 2009 evaluated specific second-line therapies for severe PPH and reported a similar peripartum hysterectomy rate (26%) [25]. Our trial was underpowered to reach statistical significance in the rate of salvage hysterectomies between treatment arms.

When this study was designed, no systematic thromboprophylaxis was recommended in women with severe PPH and no specific guidelines were available. Currently, clinical attitudes vary from the prescription of low-molecular-weight heparin, as soon as the residual hemorrhagic risk seems reasonably low enough (for instance, 24 h after cessation of PPH or later, depending on the individual situation), to no drug-based prophylaxis [26–28]. This issue will have to be carefully addressed in the design of future RCTs because the present study was not powered to assess this safety outcome (7% vs. 19%; $P = 0.11$). Two of the women (5%) in the intervention arm developed a venous thrombotic complication. In both cases, this event was associated with typical risk factors (placenta abruption, emergency Cesarean section and blood transfusion) and occurred despite thromboprophylaxis. The 5% global rate of thrombotic complications is higher than the 2.5% reported in the review by Franchini *et al.* [17]. We think that in patients with severe PPH treated with rhuFVIIa, thromboprophylaxis, which was left to the attending physician's discretion in our trial, is a major issue. Trials on the off-label use of rhuFVIIa for other indications, including spontaneous intracerebral hemorrhage, have often assessed higher doses than we did and included older patients: the frequency of venous thromboembolic events in these trials ranged between 2% and 4%, consistent with our finding [29–31].

Primary outcome assessments were based on unambiguous technical and clinical endpoints that were easy to check. Due to our limited recruiting capacities, it would have been difficult to design an RCT to demonstrate a significant rhuFVIIa-associated reduction in the number of peripartum hysterectomies, the most important and only clinical endpoint with definitive consequences. Therefore, this first RCT focused on the reduction of second-line interventional therapies.

Our trial has some significant limitations. It was an open RCT and not a placebo-controlled, double-blind trial because neither patients nor investigators were blinded to treatment. The major risk of bias was that inclusion in the standard care arm during PPH could have led investigators to perform earlier second-line interventional therapies. However, no difference in the time to second-line treatment was detected between arms.

The results and limitations of this first RCT assessing the use of rhFVIIa in severe PPH may be useful in designing a double-blind trial [26,32], which is now needed before strong recommendations can be made.

Addendum

J.-C. Gris and G. Lavigne-Lissalde had full access to all data in the study and take responsibility for the data integrity and the accuracy of the data analysis. Study concept and design: J.-C. Gris, G. Lavigne-Lissalde, A. G. Aya, F. J. Mercier, S. Bouvet and P. Fabbro-Peray. Data acquisition: J.-C. Gris, G. Lavigne-Lissalde, A. G. Aya, S. Bouvet and P. Fabbro-Peray. Data analysis and interpretation: J.-C. Gris, G. Lavigne-Lissalde, A. G. Aya, F. J. Mercier, S. Roger-Christoph, C. Chauleur, E. Morau, A. S. Ducloy-Bouthors, A. Migon, M. Raucoules, A. Bongain, F. Boehlen, P. de Moerloose, S. Bouvet and P. Fabbro-Peray. Drafting of the manuscript: J.-C. Gris, G. Lavigne-Lissalde, A. G. Aya, F. J. Mercier, S. Bouvet and P. Fabbro-Peray. Critical revision of the manuscript for important intellectual content: all authors and P. Landais. Statistical analysis: S. Bouvet and P. Fabbro-Peray. Administrative, technical or material support: Nimes University Hospital. Study supervision: J.-C. Gris, G. Lavigne-Lissalde and A. G. Aya.

Acknowledgements

We warmly thank the members of the Clinical Research Department of the University Hospital of Nîmes, namely P. Landais, C. Castelli, S. Granier, C. Masseguin, J. M. Kinowsky and C. Maillard, who showed great commitment to the technical management of the study.

This study was supported by an Academic Research Clinical Trial grant by the French Ministry of Health (Programme Hospitalier Inter-Régional de Recherche Clinique, PHRC-I/2005/GL).

Novonordisk France gave technical support for the transport of products between the promoter center (Nimes) and the other seven university hospitals in France and Switzerland. The industry had no role in: the study design and implementation; data collection, analysis and interpretation; the preparation, review and approval of the manuscript; or the decision to submit the manuscript.

Presented as an oral communication at the XIV Congress of the International Society on Thrombosis and Haemostasis, Amsterdam, the Netherlands, June 29–July, 2013.

Ethical approval

Ethical approval was obtained in each country from the relevant local or national research ethics committees. Consent to participate was obtained from the maternity units.

Disclosure of Conflict of Interest

A. G. Aya reports non-financial support from Novo Nordisk during the conduct of the study. A. Mignon reports lecture fees and grant support from Laboratoire Français Biopharmaceutique and non-financial support from Novo Nordisk during the conduct of the study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Biological results for samples collected at various times.

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