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An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage

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Background: Empirical off-label use of recombinant activated factor VII (rFVIIa) has been reported to be effective in some cases of severe postpartum haemorrhage (PPH). Successful management of these patients has lead to more wide-spread use of rFVIIa in less severe cases without any evidence for the advantages of its administration.
Methods: Until November 2006, we had administered rFVIIa to 38 parturients. Based on our initial experience with the first 12 patients, we prepared guidelines for the use of rFVIIa. During the existence of these guidelines, we made a retrospective comparison of the 26 women who received rFVIIa with another 22 women who were treated during the same time period without using rFVIIa.
Results: The total amount of blood loss was significantly higher (11.3 ± 4.5 vs. 8.0 ± 3.1 l), and the coagulation screen revealed significantly longer partial thromboplastin time (APTT) and prothrombin time (PT) values and significantly lower fibrinogen values in patients receiving rFVIIa. The need for red blood cells, platelets and fibrinogen concentrate was significantly higher in these women. Although the response was considered good in two-thirds of the women, several patients received rFVIIa with a poor or no response as a result of arterial bleeding.
Conclusion: The decision to use rFVIIa resulted from a more profound haemorrhage. We did not gain any evidence to extend the use of rFVIIa into less severe cases of PPH. Furthermore, this policy would result in a profound increase in the overall costs of the treatment. Randomized placebo-controlled trials are urgently needed to optimize the use of rFVIIa in obstetric haemorrhage.

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Key words: Recombinant factor VIIa; coagulation; postpartum haemorrhage.

THE cornerstone in the treatment of major postpartum haemorrhage (PPH) consists of the treatment of uterine atony (manual massage and uterotonic medications), removal of retained placental fragments, surgery as a result of uterine or birth canal trauma and/or effective volume replacement and transfusion therapy (1, 2). However, in case of ongoing bleeding additional interventions such as selective arterial embolization may be needed. Empirical off-label use of recombinant factor VIIa (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) has been reported to be effective in some cases of severe PPH (3–7). However, the case reports make it obvious that practise relating to the use of rFVIIa in PPH is far from uniform (7). It has been considered unlikely that randomized controlled trials will ever be performed in patients with life-threatening PPH.

The department of obstetrics and gynaecology at Helsinki University Hospital in Finland consists of three maternity units with an average annual number of 13,700 deliveries. Our unit is a tertiary referral hospital for high-risk pregnancies with 4943 deliveries in 2006; 1293 were caesarean sections. Until November 2006, we have administered rFVIIa to 38 parturients with major PPH. Based on our initial experience with the first 12 patients published previously (6), we prepared guidelines for the use of rFVIIa in massive PPH. In order to find out if we can improve our guidelines we made a retrospective comparison of 26 women who received rFVIIa during the existence of these institutional guidelines with another 22 women who were treated as a result of major PPH during the same time period but without the use of rFVIIa.

Methods

According to our guidelines (Table 1), administration of rFVIIa is not required but it should be considered

Table 1

Guidelines for the use of rFVIIa in major PPH at the Department of Obstetrics and Gynecology, Helsinki University Hospital, Finland.

Consider the use of rFVIIa when the patient has lost about 1.5 times her blood volume
Surgery and arterial ligation is preferable in cases of local profuse bleeding
If a hysterectomy is considered as a result of intractable bleeding, administer rFVIIa first in seeking to avoid uterectomy (in cases where there is no obvious indication for hysterectomy, such as abnormal placentation)
If a selective arterial embolization is proposed as a result of local uncontrolled bleeding (e.g. cervical or vaginal lacerations), do not give rFVIIa as a general rule
If a selective arterial embolization is proposed as a result of poorly defined or diffuse uncontrolled bleeding, administer rFVIIa and consider a second dose in 30 min if needed (embolization may prove unnecessary)
If the uncontrolled bleeding continues and the embolization procedure is delayed, administer rFVIIa
Before rFVIIa administration, aim to establish the following levels: Haemoglobin 70 g/l TT 40% (international normalized ratio <1.5) APTT $<1.5 \times$ upper normal range Platelets 50×10^9/l Fibrinogen 1.0 g/l (fibrinogen concentrate and/or FFP)
Prior to rFVIIa administration, always determine the haemoglobin level, platelet count and the coagulation profile (for later evaluation of the response to rFVIIa administration)
A single dose of rFVIIa is 90–120 μg/kg (19) that is: 2×2.4 mg in patients weighing <55 kg 3×2.4 mg in patients weighing 55–80 kg 4×2.4 mg in patients weighing >80 kg
After rFVIIa administration, infuse FXIII 1250 IU
In case of poor or no response, rule out localized arterial bleeding and thereafter consider a second dose of rFVIIa in 30 min
In case of severe prolonged bleeding, give a second/third dose of rFVIIa in about 2 h; and always administer 8–12 units of platelets before the third dose, irrespective of the platelet count (19)
Within 24 h after cessation of the bleeding, always consider start of LMWH

rFVIIa, recombinant factor VIIa; PPH, postpartum haemorrhage; TT, thromboplastin time; APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; LMWH, low-molecular weight heparin.

when the patient has lost about 1.5 times her blood volume. The decision to use rFVIIa or not in severe PPH is made by the senior anaesthetist after discussion with the gynaecologist. Until November 2006, 26 women had received rFVIIa during the existence of these institutional guidelines. A retrospective analysis revealed another 22 women were treated as a result of major PPH during the same time period but without the use of rFVIIa. We obtained approval from the local Ethics Committee and informed consent from each patient to perform a comparison of these two patient groups.

Patient characteristics as well as obstetric and surgical data were collected. We also noted laboratory data including haemoglobin, platelet count and the coagulation screen that is available on a 24-h/7-day basis (Table 2). In the absence of the coagulation screen, thromboplastin time (TT), activated partial thromboplastin time (APTT) and plasma fibrinogen were noted. Blood gas analysis including ionized calcium was determined just before rFVIIa administration. Patient core temperature was not measured systematically but all patients were actively warmed using a forced air warmer and all fluids and blood products were administered using one to two Hot Line™ devices (Smiths Medical MD Inc., St Paul, MA, USA).

The response to the administration of rFVIIa was defined as good if the bleeding after its administration was 1000 ml or less and no additional interventions were needed or only vaginal lacerations were sutured. The response was defined moderate if the bleeding was more than 1000 ml but no additional surgical or radiological interventions were required. The response was defined poor or missing if cessation of the bleeding necessitated a subsequent selective arterial embolization or surgical interventions (laparotomy for hemostasis and/or arterial ligation).

Results are expressed as mean values ± SD (range). The data were compared using the chi-square and the two samples, two-tailed Student's *t*-test assuming unequal variances. $P < 0.05$ was considered to be statistically significant.

Table 2

The coagulation screen and the normal range of each test at Helsinki University Hospital.

TT	70–130%
PT	17–24 s
APTT	24–40 s
Thrombin time	17–25 s
Fibrinogen	1.7–4 g/l
AT3	84–108%
FV	79–128%
FVIII	52–148%
D-dimer	<0.5 mg/l

TT, thromboplastin time; PT, prothrombin time; APTT, activated partial thromboplastin time; AT3, antithrombin-3; D-dimer, fibrin degradation products.

Results

There were no significant differences in patient characteristics or obstetric data between the groups (Table 3). The flowcharts of the women are presented in Fig. 1. Eight patients underwent a peri-partum hysterectomy before rFVIIa was used. Three hysterectomies were performed as a result of abnormal placentation, and in two additional patients, an uterectomy had been performed before the patients were transferred to our hospital. In the non-rFVIIa group, six patients underwent a peri-partum hysterectomy: one had been performed before transportation to our hospital, one was performed as a result of abnormal placentation, and in two additional patients, hysterectomy was considered unavoidable.

One or several coagulation screens were determined in 25 patients receiving rFVIIa and in 18 women treated without it. In the remaining five patients, one or several TT, APTT and plasma fibrinogen determinations were available. The laboratory data and the amount of blood loss are presented in Table 4. The coagulation screen revealed significantly higher APTT and prothrombin time (PT) values as well as significantly lower TT and fibrinogen values in women receiving rFVIIa. The total amount of blood loss and the need for red blood cells (RBC), platelets and fibrinogen concentrate were significantly higher in these patients (Table 4). However, the ratio of units of fresh frozen plasma (FFP) to that of RBC administered did not differ significantly ($P = 0.277$) between the groups (0.64 ± 0.17 in patients receiving rFVIIa and 0.73 ± 0.31 in non-rFVIIa patients, respectively).

In most women, the laboratory values at the time of rFVIIa administration were in accordance with the targets presented in our guidelines. The blood gas analysis did not reveal severe acidosis or low ionized calcium at the time of rFVIIa administration (Table 5). The response to rFVIIa was considered good in 17, moderate in 3 and poor in 6 parturients (Fig. 1).

One woman in the rFVIIa group needed intensive care unit treatment for 2 days as a result of pulmonary oedema. Furthermore, one woman in the non-rFVIIa group underwent several plasmapheresis in a high-dependency unit as a result of pre-eclampsia and the syndrome of haemolysis, elevated liver enzymes and low platelets. In all the remaining patients in both groups, the post-operative care was given in our recovery room, including one woman in the rFVIIa group who suffered a pulmonary embolism. No other severe complications were detected and all rFVIIa patients were discharged home within 3–18 days and all non-rFVIIa patients within 4–16 days, respectively (Table 3).

Table 3

Patient characteristics and obstetric data in parturients receiving rFVIIa for major PPH and in those treated without rFVIIa (mean ± SD or number).

	Patients treated with rFVIIa ($n = 26$)	Patients treated without rFVIIa ($n = 22$)	*P*-value
Age (years)	33 ± 4	35 ± 4	0.094
Height (cm)	167 ± 6	165 ± 8	0.497
Weight (kg)	78 ± 11	89 ± 21	0.056
Weeks of gestation	38 ± 3	38 ± 4	0.939
Mode of delivery			
Vaginal (*n*)	15	10	
Instrumental (*n*)	1	1	0.698
Caesarean section (*n*)	10	11	
1st/2nd/3rd/4th or more pregnancy (*n*)	12/5/6/3	12/6/1/3	0.340
Twin pregnancy (*n*)	4	6	0.312
IVF pregnancy (*n*)	6	3	0.404
Pre-eclampsia (*n*)	2	3	0.502
HELLP (*n*)	0	1	0.272
Previous endometriosis (*n*)	4	2	0.511
Main cause of bleeding			
Atony (*n*)	9	8	
Retained placenta/fragments (*n*)	5	4	0.993
Uterine or birth canal tear (*n*)	9	7	
Abnormal placentation (*n*)	3	3	
Hospital length of stay after delivery (days)	8 ± 3 (range 3–18)	8 ± 4 (range 4–16)	0.991

rFVIIa, recombinant factor VIIa; PPH, postpartum haemorrhage; IVF, *in vitro* fertilization; HELLP, syndrome of haemolysis, elevated liver enzymes, and low platelets.

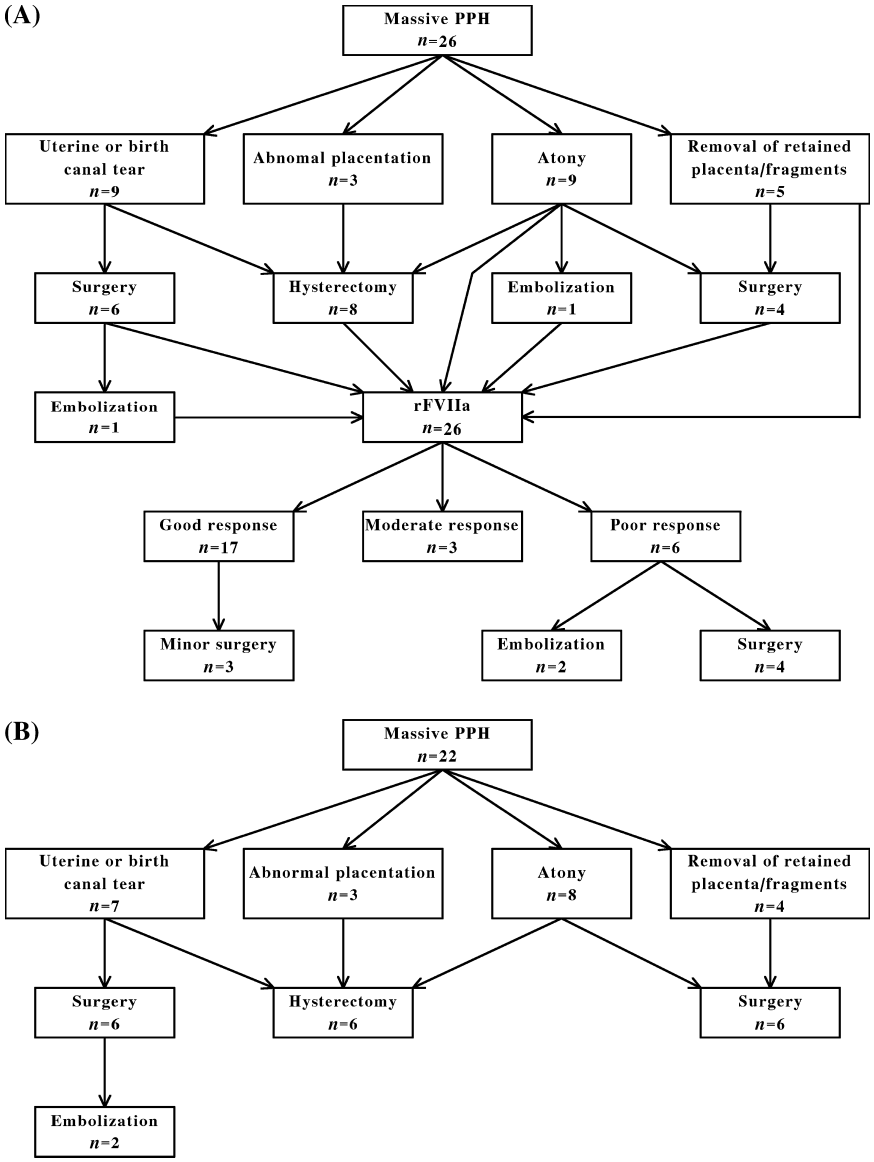

Fig. 1. Flowchart of the patients receiving recombinant activated factor VII (rFVIIa) (A) and of those treated without it (B). The patients are grouped according to the main cause of bleeding although in one woman there might have been several causes of bleeding (e.g. retained placenta/placental fragments and/or atony and/or birth canal trauma).

Discussion

Based on the amount of blood loss, the laboratory values, and the need for blood products and fibrinogen concentrate, the decision to use rFVIIa resulted from a more profound haemorrhage. Although the response was considered good in two-thirds of the women, several patients received rFVIIa with poor or no response as a result of arterial bleeding. According to our guidelines, the use of rFVIIa should be considered if the patient has lost about 1.5 times her blood volume. Therefore, we cannot assume that our policy would reduce the total number of patients with massive PPH. Furthermore, the number of patients is far too small to make any conclusion about the possible association between laboratory parameters and the response to rFVIIa administration.

The number of patients with a PPH of 1.5–5 litres was 63 at our institution in 2005. Treatment of these women with rFVIIa would have resulted in an enormous increase in the overall costs of the treatment although the bleeding would have ceased anyway. Furthermore, rFVIIa should not be used to

Table 4

Most abnormal values of laboratory tests and amount of blood loss in parturients receiving rFVIIa for major PPH and in those treated without it.

	Most abnormal value in patients receiving rFVIIa ($n = 26$)		Most abnormal value in non-rFVIIa patients ($n = 22$)		*P*-value
	Mean ± SD	Range	Mean ± SD	Range	
Haemoglobin (g/l)	56 ± 16	(30–95)	64 ± 17	(27–92)	0.126
Platelet count (10^9/l)	76 ± 35	(26–169)	78 ± 35	(18–145)	0.787
TT (%)	44 ± 17	(13–75)	55 ± 13	(34–82)	0.048
PT (s)	33 ± 12	(23–71)	26 ± 3	(22–33)	0.016
APTT (s)	74 ± 45	(41>180)	50 ± 31	(33>180)	0.015
Thrombin time (s)	41 ± 32	(21>140)	28 ± 22	(15–107)	0.154
Fibrinogen <1.0 g/l* (*n*)	$n = 11$		$n = 3$		0.029
Fibrinogen† (g/l)	1.6 ± 0.4	(1.0–2.4)	2.0 ± 0.7	(1.0–4.0)	0.062
AT3 (%)	33 ± 11	(<10–64)	35 ± 9	(20–53)	0.340
FV (%)	37 ± 19	(<7–80)	48 ± 30	(10–122)	0.190
FVIII (%)	41 ± 25	(<5–124)	55 ± 25	(<5–101)	0.099
D-dimer (mg/l)	28 ± 38	(1.6–144)	17 ± 15	(3.5–51)	0.240
Bleeding before rFVIIa (l)	9.9 ± 4.4	(4.2–19.7)			
Total bleeding (l)	11.3 ± 4.5	(4.4–20.0)	8.0 ± 3.1	(5.0–19.0)	0.005
RBC (units)	20 ± 8	(7–39)	13 ± 6	(6–26)	0.003
Platelets (units)	23 ± 12	(8–54)	14 ± 10	(8–48)	0.014
FFP (units)	12 ± 6	(4–22)	10 ± 5	(4–18)	0.074
Fibrinogen concentrate (*n*)	$n = 15$		$n = 5$		0.014
Dose of rFVIIa (μg/kg)	100 ± 14	(73–122)	–		

rFVIIa, recombinant factor VIIa; PPH, postpartum haemorrhage; TT, thromboplastin time; PT, prothrombin time; APTT, activated partial thromboplastin time; *the detection limit at our central laboratory; †in patients with plasma fibrinogen 1.0 g/l or more; AT3, antithrombin-3; D-dimer, fibrin degradation products; RBC, red blood cells; FFP, fresh frozen plasma.

compensate for an inadequate replacement therapy, and it is unlikely that it could work optimally if there is a lack of the basic and final components of the coagulation cascade. Early and effective administration of RBC, fibrinogen concentrate, FFP and platelets as well as the control of uterine atony [uterine massage and oxytocin, misoprostole, methylergometrine and sulprostone (8)] are the cornerstone of any massive PPH. These manoeuvres are essential before considering the administration of rFVIIa. The only exception is an unstable patient who has to be transferred to a hospital where more demanding surgery or a selective arterial embolization has to be performed. By eventually reducing the bleeding for a short period, rFVIIa may give some additional time for more effective replacement therapy.

Our results show that during the early phases of an instantaneous massive PPH the level of several coagulation factors remains very low and often significantly lower than needed for greater thrombin generation or effective platelet activation (9, 10). In spite of high plasma concentrations of fibrinogen prior to delivery, the level of fibrinogen decreases promptly along with the massive haemorrhage. Therefore, we suggest that 3–4 g of fibrinogen should be administered when the amount of blood loss reaches 3–4 litres and the bleeding continues uncontrolled. At that time, FFP and eventually platelets (depending on the platelet count determined before delivery) should be ordered. Administration

Table 5

Laboratory values just before rFVIIa administration in 26 parturients receiving rFVIIa for major PPH.

	Mean ± SD	Range
Haemoglobin (g/l)	86 ± 14	(51–109)
Platelet count (10^9/l)	108 ± 32	(50–169)
TT (%)	54 ± 15	(35–83)
PT (s)	28 ± 4	(22–35)
APTT (s)	53 ± 22	(24–130)
Thrombin time (s)	29 ± 9	(19–49)
Fibrinogen <1.0 g/l* (*n*)	$n = 4$	
Fibrinogen† (g/l)	1.9 ± 0.6	(1.1–3.4)
AT3 (%)	41 ± 12	(<15–67)
FV (%)	46 ± 22	(15–99)
FVIII (%)	57 ± 34	(19–150)
D-dimer (mg/l)	12 ± 14	(0.6–41)
pHa (7.35–7.45)	7.31 ± 0.06	(7.22–7.42)
BE (–2.5–2.5 mmol/l)	–6.8 ± 2.5	–(1.9–11.2)
Ca^{++} (1.16–1.3 mmol/l)	0.94 ± 0.10	(0.71–1.12)

rFVIIa, recombinant factor VIIa; PPH, postpartum haemorrhage; TT, thromboplastin time; PT, prothrombin time; APTT, activated partial thromboplastin time; *the detection limit at our central laboratory; †in patients with plasma fibrinogen 1.0 g/l or more; AT3, antithrombin-3; D-dimer, fibrin degradation products; pHa, arterial pH (normal range); BE, base excess (normal range); Ca^{++}, ionized calcium (normal range).

of fibrinogen may be important also to reverse the dilutional coagulopathy associated with the use of colloids (11). The present results show, that in case of effective replacement therapy with fibrinogen and FFP, the level of FVIII remains acceptable (9) without the use of FVIII concentrate. However, single patients with very low levels of FVIII may benefit from FVIII concentrate. In our experience, there is no room for delaying administration of fibrinogen, FFP and platelets only after the bleeding is controlled. In massive PPH, this strategy will lead to severe deficiencies of several coagulation factors where there are no prerequisites to achieve effective hemostasis by surgery or selective arterial embolization.

According to several text books, a low level of FXIII of 5–10% or less would be enough to stabilize the fibrin clot (12). However, two recent studies suggest that a level of 60% or less may be associated with increased intra-operative bleeding in various surgery or an increased risk of post-operative haematoma after neurosurgery (13, 14). We have determined the plasma concentration of FXIII in two patients the day after the haemorrhage and in one patient just prior to the use of rFVIIa. As these values varied between 34% and 50%, we changed our guidelines in 2005 by adding the infusion of 1250 IU of FXIII immediately after the administration of rFVIIa. Of course, the use of FXIII may be beneficial in major PPH irrespective of the use of rFVIIa.

Our experience also indicates that if there is no response to the first dose of rFVIIa, every effort should be made to reveal localized bleeding which should be managed by surgery or selective arterial embolization. Since 2003, four women have received two doses of rFVIIa and three of them had to undergo a subsequent selective arterial embolization. The remaining patient was transferred to our institution after a postpartum hysterectomy, and the bleeding (9.5 litres) stopped after the second dose of rFVIIa.

Recently, several studies have reported increasing rates of peri-partum hysterectomy (15, 16). Vaginal birth after caesarean section, primary and repeat caesarean deliveries and multiple births seem to be independently associated with an increased risk for peri-partum hysterectomy (16). In some patients in our series, a laparotomy and a hysterectomy may have been avoided. Accordingly, since 2001, the annual numbers of women undergoing a peri-partum hysterectomy at our institution were 11, 8, 10, 6, 7, and 7, respectively. However, it must be noticed that in rare occasions (one to two cases annually at our institution) there are women with severe unresponsive uterine atony which leads to an intractable haemorrhage of several litres of blood within 5–10 min and where an immediate decision to perform a hysterectomy is the only way of saving the woman's life.

In this series, there were two patients who underwent an angiography before rFVIIa administration both as a result of a blood loss of 14 litres. In one patient the angiography did not reveal any extravasation of the contrast material while in the other woman there was a minor suspicion of extravasation on the right side. A subsequent selective arterial embolization of uterine arteries or the right internal iliac artery did not have any impact on the bleeding. Administration of rFVIIa, however, resulted in cessation of the bleeding with no additional interventions or need for additional blood products.

In complex situations there is a risk of thromboembolic complications associated with the use of rFVIIa (17) but in previously healthy patients with major haemorrhage, the risk seems to be low even in the presence of disseminated intravascular coagulation (3). In many patients in this case series, the low level of platelets and the very low level of fibrinogen, FV, and FVIII combined with low level of antithrombin-3 (AT3) and the high amount of fibrin degradation products indicate the presence of disseminated intravascular coagulation. However, in many cases of severe PPH this phenomenon may be associated with a huge localized (pelvic) consumption of coagulation factors but not with a real disseminated intravascular coagulation. Accordingly, we have noticed that with successful management of PPH, the level of fibrin degradation products decreases promptly within 12–24 h simultaneously with a slow increase in the level of AT3 (data not shown).

In our series, there was one otherwise healthy parturient who experienced symptoms of a pulmonary embolism 17 h after the administration of rFVIIa and cessation of bleeding. Before her elective caesarean section as a result of placenta percreta, balloon catheters were inserted into both internal iliac arteries. During the planned hysterectomy and ongoing bleeding, these balloons were inflated for 2 h. After a blood loss of 8 litres, an angiography revealed no sign of extravasation of the contrast material. Recombinant FVIIa was administered and the bleeding stopped. The reason for the pulmonary embolism (verified by contrast computerized tomography) was considered multifactorial and reconsidering this case would not have changed the strategy selected. A low-molecular weight heparin (LMWH) was started and the patient thereafter recovered uneventfully. Several months after cessation of her warfarin therapy, screening for thrombophilia revealed a functional

AT3 deficiency. On the morning of surgery, the AT3 level had been normal (111%) and after cessation of the anticoagulation, the AT3 level fluctuated between slightly decreased and normal values. Screening of her close relatives confirmed the diagnosis. It must be noticed, however, that in every woman with successful management of massive PPH with or without the use of rFVIIa, administration of LMWH should always be considered within 12–24 h after cessation of the bleeding.

In patients not receiving rFVIIa, the bleeding seems to have been less instantaneous as a higher level of fibrinogen and that of other coagulation parameters was maintained with only 5 out of 22 patients receiving fibrinogen concentrate. The ratio of units of FFP to RBC administered did not differ statistically significantly between the groups. One of these women underwent an elective caesarean section and a planned hysterectomy as a result of placenta accreta, another uterectomy had been performed before the patient was transferred to our hospital, and in two additional patients, hysterectomy was considered unavoidable. However, it can not be excluded that in some of these patients, the use of rFVIIa might have reduced the bleeding and in two of them, the use of rFVIIa might have prevented the peri-partum hysterectomy. At our institution, the final decision about the use of rFVIIa is made by the senior anaesthetist. Instead of restrictions in its use, we believe that only continuous evaluation of own courses of action and frequent education of the personnel are essential to control these life-threatening situations and to achieve better results.

There is no single reason why the number of women with life-threatening PPH is not decreasing in spite of growing knowledge and better facilities to cope with these patients. In addition to the traditional factors predisposing to PPH (18), our material from the past few years shows that labouring women with previous surgery as a result of endometriosis and those with an *in vitro* fertilization-induced pregnancy possess an increased risk for major PPH. However, many of the women presenting with massive PPH are previously healthy, and therefore every maternity unit must be prepared to handle these unexpected critical emergencies.

In conclusion, in case of ongoing bleeding, every effort should be made to reveal a localized bleeding which should be managed by surgery or selective arterial embolization. Since 2003, the annual number of parturients receiving rFVIIa at our institution has been 10–12. Already now rFVIIa is annually the most expensive single drug used in our operating theatre. These results or the case reports published recently do not give any evidence to extend the use of rFVIIa into less severe cases of PPH or into its prophylactic use. This policy would result in a profound increase of the overall costs of the treatment. Therefore, our guidelines will not be changed according to these results. Furthermore, from an ethical point of view there should be no contraindication for larger randomized placebo-controlled trials in less severe or in massive PPH. These trials are urgently needed to optimize the use of rFVIIa in obstetric haemorrhage.

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