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Use of recombinant activated factor VII in severe post-partum haemorrhage: Data from the Italian Registry A multicentric observational retrospective study

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ABSTRACT

Purpose: To report the Italian real experience in clinical practice about recombinant factor VII activated (rFVIIa) in Post-Partum Haemorrhage (PPH) treatment.

Methods: An Italian retrospective survey of severe primary PPH cases treated with rFVIIa was performed. Anamnestic, clinical and haemostatic data about thirty-five patients with PPH, from 2005 to 2007, were collected. Coagulative parameters and transfusion requirements before and after rFVIIa treatment were compared.

Results: After rFVIIa administration INR was significantly decreased, while fibrinogen levels were markedly increased. Median of packed red blood cells units, platelets units, fresh frozen plasma, crystalloids and colloids needed, before and after rFVIIa administration, were respectively 6 and 2 units ($p < 1.2 \times 10^{-6}$), 1.5 and 0 units ($p = 0.001$), 1250 and 0 mL ($p < 4.4 \times 10^{-5}$), 3000 and 1250 mL ($p < 0.0042$). Twenty-nine of 35 patients needed surgical intervention before rFVIIa administration, 9/35 after treatment. Hysterectomies have been performed respectively in 10/35 cases before and in 6/35 cases after rFVIIa infusion. No maternal deaths have been reported. No adverse events or thromboembolic complications were observed.

Conclusions: Our clinical and haemostatic data suggest that recombinant activated factor VII may be a safe and helpful adjunctive therapy in the PPH management.

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Introduction

Major Post-Partum Haemorrhage (PPH) is a life-threatening labour complication, which mainly occurs without warning, predictive signs or symptoms and often in absence of predisposing conditions [1]. Severe PPH is defined by an estimated blood loss during the first 24 hours post-partum, of more than 500 mL in case of natural delivery and of more than 1000 mL in case of caesarean section [2]. In developed countries PPH incidence is reported between 0.5% and 2% [3]. In these countries it is the third cause of maternal mortality, after venous thromboembolism (VTE) and hypertension. In developing

countries, major PPH is cause of 120-000-150.000 maternal deaths every year [4]. Therapeutic strategies for severe PPH management are largely standardized. The cornerstone of massive PPH consists in uterotonic drugs administration, large amounts of colloids-cristalloids and blood components infusion to replace lost intravascular volume and to restore oxygen-carrying capacity and haemostatic competence, radiological interventional procedures as uterine or internal iliac arteries embolization or surgical conservative approach as B-lynnch suture and, finally, hysterectomy [4,5]. Nonetheless, PPH related mortality and morbidity remains unacceptably high in developed countries [4,6], contributing to hysterectomy in at least 50% of cases [7]. Several risk factors for peripartum haemorrhage have been identified, however, with limited utility for prevention of this dramatic delivery complication. A consistent prognostic advantage could derive in general from implementation of protocols for major bleeding

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management in the obstetric setting and in particular from a haemostatic treatment improvement. Uterine atony is the most common cause of post-partum haemorrhage (75–80% cases of primary PPH). Associated conditions are an overdistended uterus due to multiple gestation, polyhydramnios or macrosomia, a rapid or prolonged labour, high parity, intra amniotic infection and functional/anatomical distortion of the uterus due to fibroid, placenta previa or uterine anomalies. Genital tract trauma is the second most common cause of PPH: uterine rupture, lacerations of cervix or vagina due to precipitous or operative delivery, prolonged labour, forceps delivery and genital tract haematomas are the serious risk factors for bleeding. Other causes for PPH can be: uterine inversion detected by abdominal vaginal examination, retained products of conception due to atonic uterus, abnormal placenta (accreta, percreta, succenturiate lobe), previous uterine surgery, high parity or incomplete placenta at delivery and coagulation abnormalities due to pre-existing states as haemophilia A, Von Willebrand's disease with history of hereditary coagulopathies or liver disease, therapeutic anticoagulation with history of blood clots and acquired coagulopathies during pregnancy as pre-eclampsia, thrombocytopenia and DIC caused intrauterine deaths, severe infection, abruptio placentae or amniotic fluid embolism.

Recombinant activated factor VII (rFVIIa) is an activated factor VII form, produced from factor VII cDNA transfected into hamster kidneys. Use of rFVIIa is recommended in patients with haemophilia A, B or acquired, in patients with factor VII deficiency and in patients with Glanzmann's thrombasthenia, refractory to platelets transfusion. In case of injury, FVIIa (natural or recombinant) binds to exposed tissue factor (TF) to initiate coagulation pathway through factor X activation [8,9]. At pharmacological dosage, rFVIIa binds to activated platelets in the injury site and active factors IX and X, leading to a thrombin burst [10]. The first case of rFVIIa administration during perioperative bleeding has been reported in 1999 [11], since this time rFVIIa has been used as adjunctive therapy in the management of patients with life-threatening and critical haemorrhages caused by trauma, abdominal or cardiac surgery or urological surgery, liver transplantation, post partum [12] and any other bleeding condition leading to impairment of haemostasis. Often the results have been a success, but in some cases, when rFVIIa has been used off-label its efficacy was not as good as hoped [13].

A Italian retrospective survey of severe primary PPH cases treated with rFVIIa from January 2005 to September 2007 was performed. The aim of our study was to report the Italian real experience in clinical practice, in order to provide wide and detailed clinical information about use of rFVIIa in the management of massive primary PPH in our country and in order to evaluate the role of haemostatic therapy in the management of this severe life-threatening obstetric complication, so contributing to treatment protocols development.

Recently, the Italian health Ministry recommended to consider the use of rFVIIa in severe PPH case management as one of the therapeutic options adoptable to prevent hysterectomy (*"In case of necessity, proceed with hysterectomy, eventually trying to stop the bleeding using activated recombinant factor VII"*) [14].

Patients and methods

The protocol of "The Italian Registry on recombinant Factor VIIa in Obstetric Life Threatening Haemorrhage" was submitted to all Italian departments of obstetrics and gynaecology. rFVIIa had been used in these centres from January 2005 to September 2007 (participating centres). The protocol was approved by local ethic committees.

A Case Report Form (CRF), attached to the protocol, was filled up with all available laboratory and clinical data by the physician who has directly managed the patient, usually an obstetric-anaesthetist, a gynaecologist or an haematologist skilled in haemostasis and thrombosis. Completed CRFs were sent electronically or by conven-

tional mail to the coordinating centre. Informed consents from PPH patients were retrospectively obtained in all cases. Patient's data were recorded anonymously. The CRFs consisted of 14 paragraphs regarding the following topics: demographic details; medical and obstetric anamnesis; risk factors for PPH, pre-partum laboratory data, laboratory parameters before rFVIIa administration; causes of PPH; estimated blood loss; medical and surgical treatment previous rFVIIa administration; blood components transfused before and after rFVIIa: number of packed red blood cells (RBC), number of platelets units, fresh frozen plasma and other blood derivatives transfused before and after rFVIIa administration; rFVIIa dosage and number of infusions required; rFVIIa administration intent (life or uterus lifesaving); fluids volume consumption before and after rFVIIa infusion; ICU hospitalisation time; thromboembolic complications or other adverse reactions related to rFVIIa administration. We considered proper to be considered for statistical analysis only the parameters available for more than 50% of treated patients. Blood transfusion requirements, rFVIIa dosage, adverse effect notification were considered mandatory fields. The reduction of bleeding corresponded to a decrease of RBC transfusion in the first 6 hours following rFVIIa infusion, which has been calculated following this formula:

$$\bullet \text{ \% reduction} = 100 - (\text{nr RBC bags after last rFVIIa administration} / \text{nr RBC bags before rFVIIa}) \times 100$$

In **Table 1** the clinical response classification related to RBC reduction has been reported after rFVIIa administration.

Patient's response to treatment was examined whatever the treatment schedule: 1 or more infusions. Blood components transfusion was calculated considering respectively the period before the first rFVIIa infusion, and the first six hours after rFVIIa administration or the last rFVIIa administration in case of multiple doses. Then we compared transfusion requirements before rFVIIa treatment with transfused blood components after the last haemostatic treatment with rFVIIa. INR and aPTT ratio were considered pathologic if superior to 1.3 whereas fibrinogen was considered pathologic under 100 mg/dl. Data was extracted from the original CRF by the first author (BG) and a co-worker (BE) and were managed under the responsibility of first author. Comparison between haemostatic parameters and variation in RBC, platelet units and fresh frozen plasma (FFP) requirements, before and after treatment, were assessed through the Wilcoxon signed rank test. The difference in the requirement of blood products was considered statistically significant in case of $p < 0.05$.

Results

35 patients with PPH treated with rFVIIa were identified from 16 Italian hospitals; 4 cases were managed in 2005, 16 in 2006 and 15 within September 2007. On average, CRF were compiled in 70% of the paragraphs.

Demographic parameters

Median age at delivery was 34.5 years (23–43). Mothers race was Caucasian (32/35, 91.5%), African (2/35, 5.7%), and Asiatic (1/35, 2.8%).

Table 1
Clinical response classification.

Clinical response	RBC reduction (%) after rFVIIa
Complete (CR)	>90
Major (MJR)	50–90
Minor (MR)	30–50
None (NR)	<30

Median gestational age at delivery was 38.5 weeks (21-41); in 33/35 cases (94.3%) was single gestation and twin in 2/35 (5.7%).

Mothers had already 3 previous pregnancies in 2/35 cases (5.7%), 2 previous pregnancies in 3/35 (8.5%) and 1 6/35 (17.2%), in 24/35 cases (69%) patients were primiparae.

Anamnesis

Family history revealed 1 case of post-partum haemorrhage in a first degree relative in 1/35 patients (2.8%); no other cases of familiar haemorrhagic history suggestive for an hereditary coagulative disorder were reported. In 1/35 cases (2.8%), there was present an anamnestic personal haemorrhagic event (epistaxis and hypermenorrhoea). Two patients (5.7%) had been treated with low molecular weight heparin, at prophylactic dosages, and last administration was performed at least 16 hours before delivery.

Pre-partum laboratory

At hospital admission, haemostatic parameters were: INR prolonged in 2 cases (1.4 and 1.8); aPTT ratio increased in 3 patients (1.5, 1.7 and 2.1), 1 of these had also a pathologic INR value; fibrinogen level pathologic (100 mg/dl) in only one case, however in the same patient the INR and aPTT ratio were also both altered. No cases of severe thrombocytopenia (platelets <50.000/uL) or severe anaemia (Hb <8.0 g/dL) were found. In conclusion, at hospitalisation, INR or aPTT ratio were abnormal in 3/35 patients (8.5%) without symptoms and haemorrhagic manifestations. In one patient an asymptomatic DIC was casually identified at admission. No other significant alterations of chemical-clinical parameters were observed, except than in patients with recognized HELLP syndrome or pre-eclampsia at admission.

Mode of delivery

Caesarean section were the most common mode of delivery: urgent in 16/35 cases (45.7%) and elective in 3/35 cases (8.5%). Delivery was vaginal in 11/35 cases (31.4%) and instrumental in 5/35 cases (14.4%).

Risk factors for PPH

The following not mutually excluding risk factors for PPH were detected: multiparity (28.5%), pre-partum bleeding (11.4%), abruptio placentae (8.5%), placenta praevia (11.4%), multiparity (>3 deliveries, including the one involved in PPH, 17.2%), isolated hypertension (5.7%), pre-eclampsia (11.4%), HELLP syndrome (2.8%), chorioamnionitis (2.8%), fetal death (2.8%), anaemia of moderate degree (14.4%), fetal macrosomia (14.4%), amniotic fluid embolism (5.7%). In our study only one patient had pathologic fibrinogen level (2.8%). No risk factors were identified in 11 patients (31.4%).

Causes of PPH

The not mutually excluding leading causes of PPH were uterine atony (60%), uterine or birth canal laceration (17.2%), placenta accreta (14.4%), pre-eclampsia (14.4%), placenta praevia (5.7%), abruptio placentae (2.8%), amniotic fluid embolism (2.8%) and severe retained placenta (2.8%). In 4 cases of uterine atony there was present an associated cause: in 1 case placenta accreta, in 1 case placenta praevia, in 1 case severe pre-eclampsia and in 1 case HELLP syndrome. There was still present 1 case of uterine laceration, a concomitant cause due to placenta accreta, and 1 case of DIC due to placental fragments remnants. Three cases (8.5%) of pre-existing DIC were reported in CRF.

Medical and surgical management

Medical and surgical PPH management, before and after rFVIIa administration, is summarized in [Table 2](#). Medical treatment consisted of: oxitocyn infusion in all cases before rFVIIa administration and in 28% after rFVIIa; methylergometrine in 45.7% of cases before and in 5.7% after rFVIIa; prostaglandins in 71.4% of cases before and in 2.8% after rFVIIa. Surgical approach for PPH management before rFVIIa use, consisted in the uterine cavity revision in 15/35 patients (42.9%); haemostatic uterine packing in 14/35 patients (40%); vessel ligation, uterine or internal iliac arteries, in 6/35 patients (17.2%); haemostatic sutures in 3/35 patients (8.5%); surgical lacerations repair in 2 cases and B-lync h suture in 1 case. In 1 case an interventional radiology procedure (embolization of internal iliac artery) was performed. Only 4 patients (11.4%), after rFVIIa administration needed a surgical intervention (uterine revision).

Hysterectomy rate

Hysterectomy was performed before rFVIIa administration in 10/35 patients (28.6%), despite previous arterial ligation in 4/9 cases. In 4/25 cases (16%) it was performed between I and II dose of rFVIIa and in 6/21 patients (28.6%) after rFVIIa, [Table 2](#). Hysterectomy was needed in 13/19 (68.4%) of caesarean deliveries and in 6/16 (37.5%) of vaginal deliveries. When rFVIIa has been used with uterus lifesaving intent, hysterectomy was performed in 4/9 patients (44%).

Estimated blood loss

The median estimated blood loss before and after rFVIIa treatment were respectively 2500 mL (1000-10250 mL) and 300 mL (100-1900 mL).

Haemostatic parameters

In [Table 3](#), the INR, aPTT ratio, fibrinogen median values and percent of patients with pathologic values in blood parameters are reported, before and after rFVIIa administration.

Ph was determined before rFVIIa administration in only 8/35 patients (22.9%).

Transfusion requirement

Significant reduction was observed in transfusion requirements after rFVIIa ([Table 4](#)).

rFVIIa dosage

A single dose of rFVIIa was infused in 28/35 patients (80%), while 7/35 patients (20%) needed a second dose, on average after 130 minutes. Median dosage administered was 87.5 µg/Kg (15-127), while it was 55 µg/Kg (15-100) in the second bolus. 50% of patients treated with a single dose demonstrate a complete response, 32% a major response, 10.7% a minor response, and 7.3% no response. 57.1% of patients treated with multiple infusions showed a complete response, 14.3% a major response, 0% a minor response and 28.6% no response.

Response to rFVIIa

The response to rFVIIa is shown in [Table 5](#). Of the 4 patients not responding: 1 had acidosis (pH 7.21) at the moment of rFVIIa treatment; 1 had severe thrombocytopenia (PLT = 18.000/uL) immediately before rFVIIa infusion, 1 was treated with a very low rFVIIa dosage (20 µg /Kg). Only in 1 patient fibrinogen concentrate (4 grams) was infused previously to rFVIIa treatment, despite of the fact that 31.4% of patients showed levels of fibrinogen below 100 mg/dL before rFVIIa administration.

Table 2
Medical and surgical treatment.

Cases	Before first dose rFVIIa			Between I and II dose rFVIIa		After last dose rFVIIa		Thrompembolic Complications	Maternal Deaths
	Medical	Surgical	Hysterectomy	Hysterectomy	Medical	Surgical			
1	-	UP	-	-	-	-	-	-	-
2	OX + ME + PG	UR + UP	-	-	-	-	-	-	-
3	OX + ME + PG	UR + UP	-	-	-	OX	-	-	-
4	OX + PG	UP	-	X	-	-	-	-	-
5	-	-	X	-	-	-	-	-	-
6	OX + PG	AL	X	-	-	-	-	-	-
7	OX + PG	UR + UP	-	-	-	OX + PG	-	-	-
8	OX + PG	UP	-	-	-	-	-	-	-
9	-	UR + HS	-	-	-	-	-	-	-
10	OX + ME + PG	UR + UP + AL	-	-	-	-	-	-	-
11	OX	UP + AL	X	-	-	-	-	-	-
12	OX + ME + PG	UR + UP	X	-	-	-	-	-	-
13	OX + PG	UR	-	X	-	-	-	-	-
14	OX + ME + PG	UP	-	-	-	OX	-	-	-
15	OX + ME + PG	UR + UP	-	-	-	OX	-	-	-
16	OX + PG	UR	X	-	-	OX	-	-	-
17	OX + ME + PG	AL	X	-	-	OX	-	-	-
18	OX + PG	UR + UP	-	-	-	OX	-	-	-
19	-	EMB	X	-	-	-	UR	-	-
20	OX + ME + PG	UR	-	-	-	ME	-	-	-
21	-	-	-	-	-	-	-	-	-
22	-	-	X	-	-	-	-	-	-
23	OX + ME	AL	-	-	-	OX	-	-	-
24	OX + PG	UR	-	-	-	-	-	-	-
25	OX + PG	-	-	-	-	-	UR	-	-
26	OX + PG	UR + HS	-	-	-	-	UR	-	-
27	-	-	X	-	-	-	-	-	-
28	OX + PG	UR + UP + AL	X	-	-	-	-	-	-
29	OX + ME + PG	-	-	X	-	OX	-	-	-
30	OX + ME	UP	-	-	-	OX + ME	-	-	-
31	OX	-	-	X	-	-	UR	-	-
32	-	-	-	-	-	-	-	-	-
33	-	UR	-	-	-	-	-	-	-
34	-	UR	-	-	-	-	-	-	-
35	OX + ME + PG	-	-	-	-	-	-	-	-

OX: oxitocin; ME: methyletergometrine; PG: prostaglandins; UR: uterin revision; UP: uterin packing; AL: arterial ligation; HS: haemostatic suture; EMB: arterial embolization; X: hysterectomy performed.

Hospitalisation

The number of days of hospitalisation after delivery is not available for more than 50% of the treated patients: it has not been indicated in CRF. 18/35 patients were admitted in an Intensive Care Unit; the median ICU permanence was 2 days [1–30].

Adverse effects to rFVIIa treatment

No adverse effects were described in CRF after rFVIIa infusion. No venous (deep vein thrombosis, superficial vein thrombosis or pulmonary embolism) or arterial complications (myocardial infarction, ischemic stroke, other arterial occlusion) were observed at 28th

day after treatment. No case of maternal deaths have been observed (Table 2). Because complications were not communicated, further instrumental exams were not made.

Discussion

Our data confirm what is reported in scientific literature, regarding the lack of positive predictive value of family and personal haemorrhagic history [1,15,16]. Only in 2 of our 35 cases there was a suggestive anamnesis. INR and aPTT resulted pathologic in 11.4% of patients at hospital admission and laboratory signs of DIC were absent in all. If we consider combined family and personal haemorrhagic history, we can conclude that in 17.1% of patients a haemorrhagic disorder could have been previously suspected.

Table 3
Haemostatic parameters.

	Median [range]			% of patients with pathologic values	
	Before rFVIIa	After rFVIIa	Reduction/increase following rFVIIa (%)	Before rFVIIa	After rFVIIa
INR	1.4 [0.96 - 4.19]	1.07 [0.7 - 1.9]	↓ 23.5% (p < 0.0008)	52,2	4
aPTT	1.11 [0.88 - 2.62]	1.14 [0.64 - 1.65]	↑ 2.2%	50	33
FIBRINOGEN	107 [60 - 386]	170 [75 - 382]	↑ 58.8%	47,8	3,7

Table 4
Transfusion requirements.

	Before rFVIIa median [range]	After rFVIIa median [range]	Median reduction following rFVIIa (%)	P
RBC units [range]	6 [1-38]	2 [0-7]	66,7	< 1.2exp-6
PLT units [range]	1.5 [0-13]	0 [0-6]	100	< 0.001
FFP ml [range]	1250 [0-10500]	0 [0-4500]	100	< 4.4exp-5
*Colloids and crystalloids ml [range]	3000 [0-16500]	1250 [0-3750]	58,3	< 0,0042

* impossible to determine ratio of colloids and crystalloids, data not present in CRF.

Table 5
Reponse to rFVIIa.

	% of patients (nr. of cases)
Complete response (reduction >90%)	51.4 (18/35)
Major response (reduction 50%-90)	28.6 (10/35)
Minor response (reduction 30%-50%)	8.6 (3/35)
No response (reduction <30%)	11.4 (4/35)

In our as well as in other published series of PPH patients [1,5,16–18], caesarian section represents the mode of delivery in about 50% of cases. Caesarean cut was mostly performed in emergency and this condition is often associated with an increased risk of PPH, but it is not clear if the emergency caesarean section itself is causatively related to PPH, or if it is associated with conditions predisposing to peripartum bleeding. In the future, this topic should be verified.

Risk factors for primary PPH are known, but massive PPH is mostly of times unpredictable and several cases occur in women without previously known risk factors. However, it has been shown that the decrease of fibrinogen, within the first four hours after diagnosis of hemorrhage, is an early predictor of the severity of post-partum hemorrhage [19]. Furthermore, women with alterations of some haemostasis related variables (low levels of fibrinogen and/or von Willebrand factor and/or factor XI, platelet CD42b, TRAP-induced of platelet CD41a, blood 0 group), are prone to develop severe forms of PPH [20].

Uterine atony was the main cause of PPH, followed by abnormal placentation, DIC, birth canal laceration, pre-eclampsia and amniotic fluid embolism. In 1/5 of cases there was present an associated cause of post-partum bleeding. Uterine atony was also reported by other authors as the leading, and often unpredictable PPH cause, accounting for 52%–82% of obstetric bleedings [1,15,16]. Abnormal placentation, DIC, birth canal laceration and retained placental fragments are other significant causes of PPH, identified in the published case series [1,15,16,21]. In our opinion it is important to underline that, excluding DIC, whatever the severe obstetric haemorrhage cause, when at least one blood volume has been lost and replaced, a dilutional coagulopathy probably occurs. One blood volume rapidly replaced with RBC and colloid/ crystalloids might be associated with a decrease of clotting factor levels below 30%, anaemia contributing to impair platelet responses and leading to the onset of dilutional coagulopathy. In presence of low fibrinogen levels before bleeding, dilutional coagulopathy can develop even before that one volume blood has been lost [22]. Therefore, the haemostatic therapy role becomes strategic in this setting and a simple volume replacement with fluids and massive transfusion is not sufficient to manage an acquired haemorrhagic disorder.

DIC is one of the most challenging situations in critical bleeding, requiring aggressive and balanced haemostatic approach. There has been reported a prevalence of DIC between 70% [1] and 88% [16] in PPH - rFVIIa treated patients series. In obstetric patients with DIC, treated with full doses of rFVIIa, no cases of coagulopathy worsening have been reported and mostly of times a significant improvement has been reported [1,15–18] in absence of thromboembolic complications. The uterotonic agents role, during obstetric bleedings, is well established in the clinical practice, however, the level of evidence and the strength of recommendation are based primarily on consensus and on expert opinion (Level C) [23]. Moreover, prostaglandins E2 (PG E2) administration, may be associated with cardiac complications when used in obstetric emergencies [24–26]. We do not fully rely the estimated reported blood loss, since we have observed significant discrepancies between the declared blood loss and the transfusion requirements. Our observation is confirmed by the comparison of blood loss and blood components consumptions reported in the published case series [1,15,16,21,27]. With this purpose, we have found extremely interesting the data reported by Bose, who showed a significant discrepancy between the real blood loss and the estimated blood loss with a significant under-evaluation of the real blood loss in

41.6% of cases [28]. Differently from other reported studies, in which the clinicians subjectively had to describe the rFVIIa effect to estimate bleeding reduction [1], our retrospective study, we decided to adopt transfusion support as an indirect and reliable blood loss indicator. Consequently, RBC support reduction is strictly and proportionally related to blood loss decrease (haemorrhage improvement). In our opinion, the decision for the requirement of a second dose of rFVIIa must be based on blood loss and on changes in vital and haemodynamic parameters. Our suggestion is to establish the recombinant factor VIIa efficacy in bleeding control through a quantitative assessment of transfusion requirement reduction, especially RBC. Clearly, formal assessment of effectiveness must be based also on clinical outcome (including hysterectomy, maternal complications, morbidity and length of the hospitalisation or ICU permanence). As reported in other case series [1,16,17,21], still in our retrospective study, we have observed that despite a high prevalence of patients with hypofibrinogenemia, only in a few of these patients, fibrinogen concentrates have been administered. Moreover, it is remarkable that only in less than 1/4 of Italian patients treated, pH had been determined before rFVIIa administration. This determination is crucial for rFVIIa efficacy, since it is well known that rFVIIa activity is severely impaired by acidosis [29].

In our retrospective study, half the patients bleed despite normal values of INR and aPTT values and, moreover, they were responders to rFVIIa. In our opinion, abnormal values of INR and/or aPTT ratio cannot be considered mandatory pre-conditions, in medical protocols, for critical bleeding treatment. According to Charbit et al. [19], still in our study, INR and aPTT are not specific for predicting blood loss, but, conversely, a simple fibrinogen measurement can anticipate the risk of severe bleeding in PPH. Now it is important to underline that it has been shown that acidosis (pH below 7.2), thrombocytopenia (platelets <50,000/uL), hypofibrinogenemia (fibrinogen <100 mg/dL), hypothermia (corporeal temperature under 35 °C) and hypocalcemia are responsible for a decrease of the rFVIIa efficacy above 90% of its activity [30]. Normalization of the fibrinogen plasma levels is of fundamental importance to ensure rFVIIa efficacy, since it has been recently demonstrated that the onset of fibrin formation and thrombin generation are shortened after rFVIIa addition, but fibrin clot strength is increased after fibrinogen supplementation. In vitro clot formation is improved by using both rFVIIa and fibrinogen [31]. Therefore, these must be considered obligatory pre-conditions in every rFVIIa treatment protocol. Tranexamic acid (TA) is often listed as an option to be considered in the management of critical bleeding. The evidence for the use of TA in PPH is very limited, however, it is reasonable to hypothesize its efficacy also in this setting, since it has been demonstrated that TA reduces the need for blood transfusion by 30% in surgery [32]. We disappointingly report the fact that in the Italian Registry only in 2/35 cases TA has been administered.

Our retrospective study showed that, before rFVIIa administration, the necessity of surgical intervention to stop haemorrhage is higher than after administration (10 cases vs 6 cases). It also showed that sometimes surgical interventions or hysterectomy were not sufficient to decrease haemorrhage; in these cases rFVIIa administration resulted a fundamental adjunctive therapy to stop massive bleeding. Considering the fact that 19/35 patients required further approaches after rFVIIa shot, it must be specified that: a) in 11/19 cases uterotonic agents (oxitocin and prostaglandins) continued to be administered at lower dosages as part of the standard protocol of medical PPH management, for four to six hours after haemostatic treatment; b) in 4/19 patients, uterine revision was performed following an obstetric indication and not as a measure to stop bleeding; c) in 6/19 patients, hysterectomy was considered mandatory: four of these patients were no responders, two were minor responders. Thus we can state that no further treatment was really needed in six patients (all of which were minor or no responders) and that it consisted in hysterectomy. However, it must be underlined that in at least three of these, rFVIIa

was infused in presence of conditions negatively affecting treatment efficacy (acidosis, thrombocytopenia, low rFVIIa dosage).

In this study no cases of bleeding related maternal death were reported. However, since there are several PPH causes, it has been hypothesized that some of these can be pathogenetically predisposing to hysterectomy, thus confounding the efficacy of rFVIIa as an uterus lifesaving approach. In the Italian Registry, we have observed a global hysterectomy rate similar to that reported in other series, however, the prevalence of this surgical approach was significantly higher in case of caesarean delivery. In our and in other studies, the numbers are still too small, to permit a stratification of the rFVIIa efficacy for each cause of PPH. We hope that in the future therapeutic haemostatic algorithm will be implemented to optimize the rFVIIa role and worldwide registries will be developed. It could allow a better understanding of the role and the dosages of rFVIIa related to PPH cause. Clinical reports and haematologic data suggest a significant clinical improvement for more than 80% of the women with severe PPH after rFVIIa administration and very few adverse effects. However, in absence of an adequate control group, any attempt to comment on the true effectiveness of the drug should be avoided. Alfirevic reported that, despite rFVIIa use, 75% of women were admitted to intensive care units; 4.4% of women died, and further 53% needed laparotomy (including hysterectomy in 61% of cases) [1]. Bouma observed a relevant reduction or complete bleeding cessation after rFVIIa (89%), 11.1% of patients died (death not related to rFVIIa) and 3.7% of patients developed thromboembolic complications [16]. Sobieszczyk reported a bleeding stop in 72% of cases, a marked reduction in 8%, a reduction in 16% of cases, 8% of maternal deaths and no thromboembolic complications [17]. Cumulatively considering all the published papers regarding haemorrhagic obstetric patients treated with rFVIIa, including our experience, thromboembolic complications are accounting for 1.5% of cases (4/261) and consist in episodes of DVT of the legs [1,16–18,21,27]. In order to demonstrate if rFVIIa is effective and safe, randomized control trials are needed, however, main cause of clinical issues in this setting, interventional placebo controlled trials in primary PPH cases are extremely difficult to perform. Although no prospective, randomized clinical trials have been conducted, several case series and retrospective case audits are suggestive for efficacy and safety of rFVIIa in the maternal population. These cases demonstrate that rFVIIa is currently being administered both as initial therapy and as a lifesaving therapy in women with life-threatening primary PPH [33]. It is also important to point out that rFVIIa use reduces costs of therapy and use of blood derivatives: in UK mean cost of blood components used in a single case is £. 6255, while rFVIIa cost for every patient in treatment is £. 3655 [34], in Italy a single bolus of rFVIIa 60 µg/kg economically corresponds to 14 packed RBC. Therefore the rFVIIa administration in massive transfusion setting remains an opportunity for transfusion medicine physicians.

Conclusions

rFVIIa administration represents a safe haemostatic approach in the management of severe PPH cases, when other conventional medical, surgical and radiology interventional approaches have not been successful. Data from Italian Registry, as well as from other case series, demonstrate the rFVIIa efficacy to reduce or stop obstetric critical bleeding. The use of rFVIIa as lifesaving therapy in cases, in which medical and surgical standard approach have failed, should be always considered as life well as uterus lifesaving treatment.

Appendix A

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