Critical bleeding in pregnancy: a novel therapeutic approach to bleeding

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A B S T R A C T

Critical post-partum hemorrhage (PPH) occurs in 1/1,000 deliveries; hysterectomy 1/2,000; risk of death 1-2/100,000. The majority of the PPH have obstetrical causes, most frequently atony of the uterus. Hereditary and acquired hemostatic defects are very rare. The therapeutic intervention, to control the bleeding and its consequences, should be as early as possible. Guidelines of standard surgical and medical measures are available. rFVIIa has been successfully used in hemophilic patients with inhibitors and in critical bleeding of different causes. Preliminary anecdotal reports of its use in PPH after failure of conventional standard therapy suggest that rFVIIa should be administered as early as possible before the consequences of severe and intractable bleeding set in.

Critical bleeding in pregnancy is defined by: 1) the amount of blood loss, 2) the rapidity of onset, 3) the blood loss related symptoms and signs. Table 1 summarizes the current definitions.[1,2,3] The bleeding can set in a series of events conducive to metabolic complications, hypoxia, disseminate intravascular coagulation (DIC), organ damage and multiorgan failure (MOF), progressively exhaustive. The criterion of the intervention to control the bleeding is therefore clinical: therapy must be instituted before successive complications ensue. In this presentation we focus on activated recombinant factor VII (rFVIIa).

Relevance of the problem

According to the World Health Organization pregnancy-related deaths are approximately 510,000/year world-wide; 25% are due to severe bleeding of any cause[4] occurring in the post partum period. In the developed world the frequency of life threatening postpartum hemorrhages (PPH) is one in 1,000 deliveries[5,6] with a risk of death of 1-2/100,000 deliveries.[3,7] Hysterectomies for intractable bleeding are 1/2,000 deliveries;[8,9] therefore hysterectomy is carried out in approximately 50% of the cases of life threatening PPH.

Etiology

The majority of the PPH have obstetrical causes, most frequently atony of the uterus.[3] Hemostatic hereditary defects are very rare (Table 2); acquired defects are uncommon. Acquired hemophilia (AH) is a rare clinical syndrome characterized by the sudden onset of bleeding in patients with a negative family and personal history, either spontaneous or after surgery or trauma, usually severe (87% of the cases) often fatal (8-22%). The depletion of factor VIII, much less frequently of factor IX, is mediated by specific autoantibodies, directed against functional epitopes with neutralization of FVIII or IX and/or its accelerated clearance from the plasma. The incidence of AH varies between 0.1 and 1.0 per million/population per year, although it is likely that not all patients are included in the published surveys. AH is commonly associated with a variety of clinical conditions: autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, asthma), solid tumours, lymphoprolipherative diseases, drug hypersensitivity and pregnancy but in 50% of the cases is idiopathic. Pregnancy is a frequent concomitant condition (7-21% in different series of AH). In general the inhibitor occurs in the first pregnancy and does not recur, although recurrence in

Table 1. Current definitions of critical bleeding in pregnancy.

Author	*Definition*
Macphail S[1]	- loss of one blood volume in a 24-hour period or transfusion of more than 10 units of blood within a 24-hour period
Sobieszczyk S[2]	- blood loss >150 ml/min (within 20 min causing loss of more than 50% of blood volume) - sudden blood loss >1,500-2,000 ml
Bouwmeester PW[3]	- reduction in Ht by at least 10% associated with hemodynamic changes

Table 2. The prevalence of hereditary and acquired hemostatic defects in general population.

Bleeding disorder	*Approximate prevalence (one case per)*
Factor VII deficiency	500,000
Factor X	500,000
Factor V	1,000,000
Factor XI deficiency	rare except in Jewish descent
Factor II	very rare
Von Willebrand disease (type 1)	100
Acquired hemophilia	1,000,000
Glanzmann's thromboasthenia	1,000,000

subsequent pregnancies was reported in some series10. In the survey carried out in Italy in 2001, 28 new cases of AH were registered (50% of the expected) and 2 were postpartum.[11] The inhibitor is in general identified on occasion of overt bleeding in the peripartum period but the time of its development in the absence of bleeding signs cannot be retrospectively determined. It may also occur up to 12 months after delivery or more rarely during pregnancy.[12] The prolonged APTT value with a normal prothrombin time, is crucial for the diagnosis.

The subsequent determination of factor VIII/IX deficiency in general is readily available in a reference laboratory. The diagnosis of PPH related to AH must never be an emergency diagnosis because the APTT value must be routinely known before delivery and the eventual possibility of bleeding predicted. DIC is a component of the complex derangement induced by the severe bleeding. DIC can either complicate the control of bleeding because of the thrombocytopenia and the depletion of the coagulation factors, or occur as an additional factor of organ dysfunction through the microvascular damage and thrombosis. The tests indicative of DIC are increased fibrin-fibrinogen degradation products (FDP) or D-dimer thrombocytopenia and hypofibrinogenemia absolute or relative to the initial values, decreased antithrombin (AT), and presence of schistocytes in the peripheral blood smear. The laboratory data must be interpreted, as usual, in the contest of the clinical picture.

Focus on rFVIIa to control the critical bleeding in PPH

The intervention to control the bleeding and its consequences should be as early as possible. The underestimation of blood loss, the inadequate volume replacement and correction of the metabolic abnormalities and the eventual delay of surgery are the avoidable causes of mortality.[1] Guidelines of standard medical and surgical measures are available.[1]

The FVII is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues, synthesized in the liver. The role of FVII in the hemostatic process is synthesized in the Figure 1. The interaction between tissue factor (TF) and FVII primes the coagulation process at the site of injury. The complex TF/ FVIIa activates factor X (FX) to FXa which in turn activates prothrombin to thrombin. rFVIIa is structurally similar to human plasma-derived FVIIa.

Its activity occurs mainly at the site of injury: systemic activity is absent or of low grade even with the administration of large doses in patients without

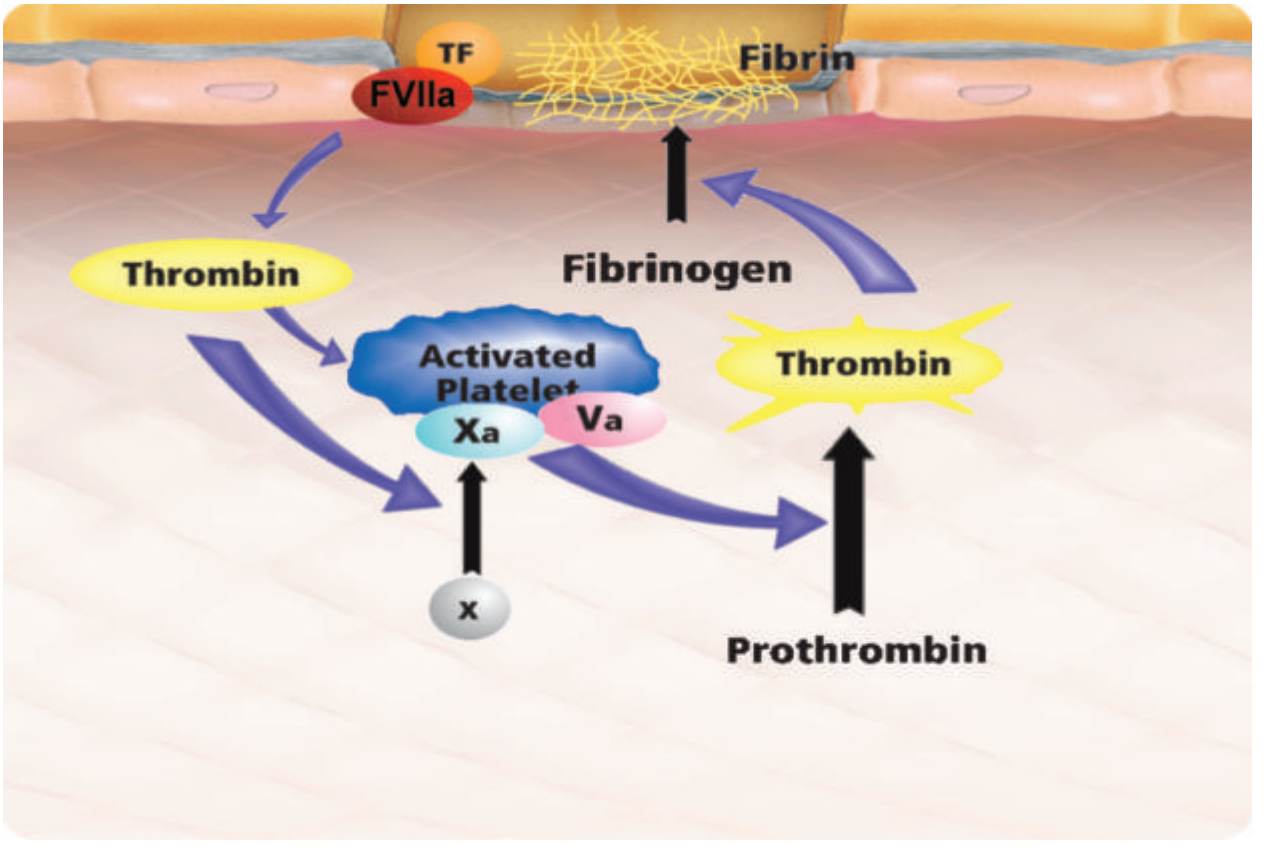

Figure 1. Tissue factor (TF)/FVIIa primes the coagulation process at site of injury. The complex TF/FVIIa activates factor X (FX) to FXa on the surface of locally activated platelets whit thrombin generation independently of FVIII and FIX (intrinsic pathway). The thrombin leads to the formation of a stable clot.

coagulopathy. Pharmacokinetic data were determined by single-dose infusion: the t1/2 was 2.3 hours (range 1.7-2.7), the median *in vivo* plasma recovery was 44% (range 30-71).[13] There are currently no satisfactory tests for monitoring the clinical effectiveness of rFVIIa. Prothrombin time, APTT and plasma FVII activity may give different results with different reagent and do not correlate with clinical events.

Indications and efficacy of rFVIIa

The approved therapeutic indications of rFVIIa in Europe are: congenital hemophilia with inhibitor, acquired hemophilia (non hemophilic patients with FVIII/FIX inhibitors), congenital deficiency of FVII and Glanzmann's thromboasthenia with the concomitant presence of anti GP IIb-IIa antibodies.

rFVIIa has been successfully used in critical bleeding of different causes (Table 3);[14-28] no comparative clinical trials and world-wide compassionate programs have shown its efficacy. The recommended dose is 90 mcg/kg every 2 hours but the dose and administration interval are adjusted on the severity of bleeding and the degree of clinical hemostasis achieved.[29] The early reports on the use of rFVIIa in gynecology date back to year 2,000. Lafflan *et al.,* reported on a case of intractable postoperative bleeding following anterior exenteration for recurrent cervical cancer.[30] White reported on a case of endometrial ablation in a patient with intractable menorrhagia due to hereditary FVII deficiency.[31] A computerized literature search was carried out in PubMed and Ovid for papers published between 2001 and 2005 in the English literature reporting on life-threatening PPH (Table 4) treated with rFVIIa after failure of conventional therapy, including hysterectomy.[32-42] Controlled or reduced bleeding was reported in 38 out of 39 patients.

Safety of rFVIIa

Systemic administration of rFVIIa carries a very low risk of thromboembolism. From 1996 to 2004 more

Table 3. Successful experience with rFVIIa in critical bleeding in non-approved indications.

Author	*Clinical conditions*
Berntorp E[14]; Lin J[15]; Brody DL[16]; Deveras RA[17]	Reversal of oral anticoagulants
Mayer S[18]	Spontaneous CNS hemorrhages
Bianchi A[19]	Extensive burns
Henke D[20]	Diffuse alveolar hemorrhage
Moisescu E[21]	Bleeding from renal failure
Ejlersen E[22]; Thabut D FR[23]	Bleeding from oesophageal varices
Kenet G[24]; Martinowitz U[25]; Dutton RP26 ; Hoyt DB[27]	Polytrauma
Pihusch M[28]	Bleeding after stem cell transpant

Table 4. rFVIIa in postpartum hemorrhage after failure of conventional therapy, including hysterectomy (data from 2001 to 2005).[32-42]

Number of papers	11
Number of patients	39
Causes of bleeding	atony 8; HELLP 7; placenta abnormalities 8; laceration 7; uterus rupture 5; other 4*.
DIC	18
Hysterectomy	24
rFVIIa number of doses (median and range)	1 (1-3)
rFVIIa dose μg/kg (median and range)°	90 (16.7-120)
Bleeding	controlled 29; reduced 9; failure 1.

** Initial cause not reported; ° Cost for a ~60 kg woman: single dose of 6 mg, approximately 6,400€.*

than 700,000 standard doses of rFVIIa were administered to several thousands patients with hemophilia and inhibitors and to patients with other bleeding disorders. The incidence of serious adverse events, including myocardial infarction, stroke, pulmonary embolism and DIC, was 1%.

Their relationship to the treatment was doubtful either because of the time-event relationship or the presence of predisposing comorbid conditions (diabetes, atherosclerosis, hypertension).[43-46]

Comments

The early intervention to control the critical PPH at the onset is crucial. The attempt to stop the bleeding is the attempt to interrupt a series of events that can be irreversible. The limited clinical experience referred to indicates that rFVIIa is an active agent. More studies are certainly necessary. The high cost of the drug should not discourage its clinical use because it may be compensated by the eventual high cost of the critical patients care.

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