RECOMBINANT ACTIVATED FACTOR VII IN OBSTETRICS & GYNAECOLOGY

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ABSTRACT

Originally developed for the treatment of bleeding in patients with haemophilia A or B and inhibitors over the past ten years, it has been successfully used to prevent or control bleeding in several other nonhaemophilic bleeding conditions. Unresponsive to conventional therapy to control excessive bleeding and reduce the exposure to allogenic blood. These include intracerebral haemorrhage, oral anticoagulant-induced haemorrhage, thrombocytopenia, bleeding associated with hepatic failure, major surgery, trauma and life-threatening obstetric and gynaecological haemorrhagic complications.1,2,3,4,5,6,7,8,9,10 These two latter ‘off label’ clinical applications of rFVIIa will be discussed in this review. Data were identified by searches of the published literature, including PubMed, references from reviews and abstracts from the most important meetings on this topic.

KEYWORDS

Factor VII, Activated Factor VII.


INTRODUCTION/METHOD

In a cell-based in vitro model, it has been shown that the addition of increasing amounts of rFVIIa (Between 50 and 150 nm) to activated platelets in the presence of FX produces a linear increase of generation of FXa independently of the presence of TF on the platelet surface.11 This dose–response mechanism can lead to the generation of significant amounts of thrombin even in the absence of FVIII and FIX, thus explaining the mechanism of action of rFVIIa in those with haemophilia. The direct activation of FIX on activated platelets in the absence of TF, resulting in improved thrombin generation, may also explain the mechanism of action of rFVIIa in acquired coagulopathy following trauma, surgery or other events.12 Moreover, the binding of rFVIIa to activated platelets may explain why rFVIIa is localised only to the site of bleeding.10 However, an alternative TF-dependent mechanism of action of rFVIIa has been proposed.13,14 In fact, according to this model, the local function of rFVIIa is mediated by the combined effect of TF expression and platelet accumulation at the site of a vascular lesion.

Lisman and De Groot11 analysed the experimental data available and concluded that both the proposed mechanisms of actions of rFVIIa (i.e. TF dependent and TF independent) are plausible. In fact, if the TF pathway is usually required for the action of rFVIIa, a rFVIIa-mediated thrombin generation can also occur on the activated platelet surface independently of TF. Moreover, the same authors observed that the enhanced thrombin generation from rFVIIa not only accelerates clot formation but also inhibits fibrinolysis by TAFI activation and enhances platelet adhesion and aggregation under flow conditions.15,16 This latter evidence may explain the therapeutic effect of rFVIIa in patients with thrombocytopenia.

In conclusion, according to the current knowledge, rFVIIa induces haemostasis by enhancing thrombin generation on thrombin-activated platelet surfaces, thereby providing the formation of a stable fibrin clot, which is resistant to premature fibrinolysis.

The use of rFVIIa in Postpartum Haemorrhage

Severe postpartum haemorrhage (PPH) remains an important cause of maternal mortality. The treatment of life-threatening PPH still remains challenging, and hysterectomy or surgical ligation of the internal iliac arteries bilaterally may be required to control the bleeding. The first-line standard treatment includes both surgical and medical (i.e. replacement transfusion therapy and uterotonic drugs) measurements to control blood loss.8,17,18,19,20,21 However, additional interventions may be needed in cases with continuing bleeding. In recent years, new therapeutic measures to control the bleeding have gained attention. In particular, there is an increasing number of case reports where empirical ‘off-label’ use of rFVIIa has been effective in the treatment of massive PPH which did not respond to conventional methods.

The first case report of successful treatment of intractable obstetric haemorrhage in a woman without haemophilia using rFVIIa was published by Moscardo et al who reported that rFVIIa successfully controlled life-threatening PPH after caesarean section in a woman who developed severe disseminated intravascular coagulopathy (DIC), liver dysfunction and renal failure. Breborowicz et al. reported seven cases of peripartum haemorrhage treated with rFVIIa. In all but one woman, a single relatively low dose of rFVIIa (Range 16.7–48 microgram/kg) was effective in controlling bleeding. Tanchev et al reported four cases of severe bleeding associated with uterine atony which were successfully treated with rFVIIa. Boyer-Neumann et al. Reported the successful management of caesarean section and the postpartum period using the sequential combination of recombinant FVIII and rFVIIa in an allimmunised woman with type 3 von Willebrand’s disease.

The largest case series is that reported by Ahonen and Jokela who presented 12 cases of severe PPH treated with rFVIIa in addition to standard surgical and medical interventions, and a good response was obtained in 11 of these cases.In 5 of these 12 cases, hysterectomy was performed.
before the administration of rFVIIa. However, as rFVIIa was effective in avoiding hysterectomy in 7 women, the authors concluded that in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery. The median dose of rFVIIa administered was 65.9 microgram/kg. However, when the cases of congenital FVII deficiency, which are known to require significantly lower doses of rFVIIa, were excluded from the analysis, the median dose of rFVIIa administered was 72.9 microgram/kg. In most cases (73%), only a single dose of rFVIIa was required.

Sobieszczynk and Breborowicz recommend a dose of rFVIIa of 40–60 microgram/kg which may be repeated if there is a lack of clinical improvement within 15–30 minutes from the initial administration of the drug. rFVIIa has also been successfully used for prophylaxis of peripartum haemorrhage in pregnant women with inherited coagulation disorders. Only a few cases have been described in the literature, mostly in women with Glanzmann’s thrombasthenia and FVII deficiency. As expected, the doses used were lower than those required for women with acute postpartum bleeding.

The use of rFVIIa in postpartum acquired haemophilia A
Among the coagulation disorders associated with PPH, postpartum acquired haemophilia A deserves a particular mention. In fact, postpartum development of an inhibitor against FVIII is a rare but severe complication of pregnancy. Overall, postpartum FVIII inhibitors constitute 7–21% of acquired haemophilia A cases. 31 Pregnancy-associated FVIII inhibitors must be recognised early to decrease maternal morbidity and mortality. Since women with acquired inhibitors do not usually have a personal or family history of bleeding episodes, it is the presence of unexplained excessive and/or prolonged vaginal bleeding or large soft-tissue haematomas from multiple sites during the postpartum period that may lead the obstetrician to suspect a coagulation inhibitor. The laboratory diagnosis of acquired haemophilia A is based on the demonstration of an isolated prolongation of the activated partial thromboplastin time, not corrected by incubating the patient’s plasma with equal volumes of normal plasma (Mixing study), associated with a normal prothrombin time, reduced FVIII levels and formal evidence of a FVIII inhibitor in a patient with no previous personal or family history of bleeding. The diagnosis of an inhibitor is confirmed by specific assays of the factor and the inhibitor using the Bethesda assay.

Acquired postpartum haemophilia A may occur following any pregnancy but is more common in primigravidas. It arises most commonly from 1 to 4 months after delivery, but it may occur as late as 1 year afterwards. FVIII inhibitors have rarely been detected during pregnancy or labour, but when they do occur during this period, they are frequently associated with severe uterine bleeding. Vaginal bleeding is the predominant symptom if the inhibitor develops within 24 hours after delivery, while ecchymosis and soft-tissue bleeding are more frequent if the postpartum FVIII inhibitor appears later. The initial aim of management is to control acute bleeding, while the long-term aim is to accelerate eradication of the inhibitors.

While the latter objective may be obtained with immunosuppressive therapy (i.e. corticosteroids and/or cytotoxic drugs), the therapeutic options used to control bleeding include agents which can increase plasma FVIII levels (i.e. desmopressin and FVIII concentrates) in clinically mild cases with low inhibitor titres and by-passing agents (i.e. activated prothrombin complex concentrates and rFVIIa) in patients with high-titre FVIII antibodies and severe bleeding. Mazzucconi et al. described four postpartum inhibitor cases treated with high-dose immunoglobulin and dexamethasone; in two women, bleeding symptoms were stopped by the concomitant use of rFVIIa at a dose of 90 microgram/kg every 12 hours for 4 days.

The use of rFVIIa in Gynaecology
With regards to the use of rFVIIa in gynaecology, there is an increasing number of reports documenting its effectiveness in controlling intractable postoperative bleeding. Panel et al. described a case of successful treatment of massive intra-abdominal haemorrhage complicating debulking surgery for advanced ovarian cancer with rFVIIa. In fact, after the administration of two doses of rFVIIa 20 microgram/kg, the woman fully recovered with no further blood loss and complete restoration of haemostasis. Sajdak et al. reported two cases of successful use of rFVIIa in gynaecological oncological patients (Endometrial cancer and vaginal sarcoma) without pre-existing coagulopathy and concluded that rFVIIa may be an important and effective drug in severe bleeding in gynaecological oncology.

Similarly, Erikci et al. reported the successful treatment of an episode of severe uterine bleeding after chemotherapy in a woman with acute myeloid leukaemia. Ciaccia et al. reported four postmenopausal women who each received rFVIIa (dose range, 17–70 microgram/kg) to control severe postoperative haemorrhage associated with elective hysterectomy for benign uterine fibroids, carcinoma of the endometrium, cervical and uterine cancer, or metastatic carcinoma of the genital tract. Bleeding resolved within 12 hours in three women after a single dose of rFVIIa. In the woman with metastatic disease, bleeding was markedly reduced after each of two doses of rFVIIa and resolved completely within 12 hours of the second dose. So far, 14 cases have been described mainly involving women operated for gynaecological cancers.

However, in one case, the drug was used for an episode of intractable menorrhagia secondary to congenital FVII deficiency and in another case as a prophylaxis in a woman with Glanzmann’s thrombasthenia undergoing surgical removal of a pelvic mass. The median dose of rFVIIa administered in the 14 cases reported was 51.6 microgram/kg, while the median number of doses injected was 1.8 (in one case, 36 rFVIIa was administered in continuous infusion). Overall, the data suggest that rFVIIa may offer an effective means of controlling bleeding associated with gynaecological surgery when conventional surgical and pharmacologic measures are unsuccessful.

Safety
The safety of rFVIIa in massive PPH and gynaecological bleeding is an issue of concern, especially with the recent report of a high rate of thromboembolic adverse events after the use of rFVIIa in women without a pre-existing coagulopathy. Although the analysis of the 79 cases treated with rFVIIa for severe obstetric and gynaecological bleeding in the reported literature revealed no thrombotic episodes, we recommend particular caution in using this drug in women at
higher thrombotic risk such as those with PPH and systemic activation of coagulation or with gynaecological cancers.

CONCLUSION
In conclusion, due to the paucity of published data, we advise the physicians to follow the currently accepted recommendations, with regards to the dose and timing of rFVIIa administration and to monitor closely such women not only for the clinical efficacy but also for the onset of adverse events.

Although supported by few and uncontrolled studies, on the whole, the published data suggest a potential role of rFVIIa in the management of obstetric and gynaecological intractable bleeding, however, further evidence is needed to improve the assessment of its optimal dose, effectiveness and safety in such conditions.

REFERENCES