The use of recombinant activated factor VII in platelet disorders: a critical review of the literature

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Introduction

Recombinant activated factor VII (rFVIIa, NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is a haemostatic agent that was originally developed for the treatment of haemophiliacs with inhibitors and then used successfully for treating haemorrhages in patients with acquired haemophilia[1-4].

In the last few years, rFVIIa has also been used with benefit as a "universal haemostatic agent" in many other non-haemophilic bleeding situations including congenital factor VII deficiencies, hepatic failure, liver transplantation, surgery and trauma[5-7].

The haemostatic effect of pharmacological doses of rFVIIa seems to be that of enhancing the rate of thrombin generation on thrombin-activated platelet surfaces, thus providing the thrombin necessary for the formation of a stable fibrin haemostatic plug[8]. Based on this information, rFVIIa has also been employed in disorders characterised by impaired thrombin generation, such as quantitative and qualitative platelet defects[9]. Figure 1 illustrates the mechanisms of action of rFVIIa.

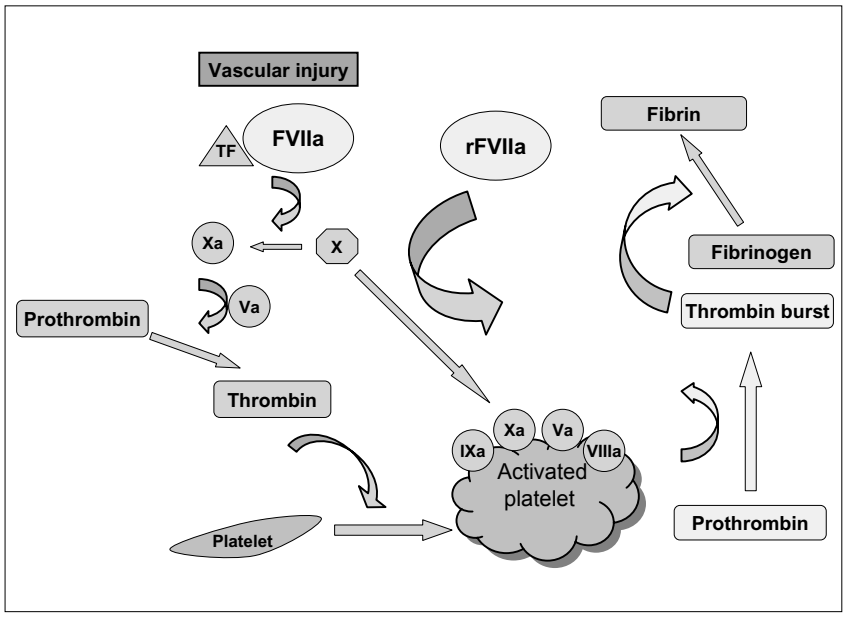

Figure 1 - Mechanisms of action of rFVIIa
Following injury to a vessel, exposed tissue factor (TF) forms a complex with factor VII activated (FVIIa). The TF-FVIIa complex activates FX leading to the conversion of prothrombin to thrombin. The initial limited amount of thrombin formed subsequently activates FVIII, FV and platelets so that the tenase complex (FVIIIa/FIXa) and the prothrombinase complex (FXa/FVa) assembled on the activated platelet surface lead to full thrombin generation. Besides this TF-dependent mechanism there is a second pathway which involves a TF-independent mechanism. In fact, recent data suggest that rFVIIa at high pharmacological doses can activate FX directly, thus leading to an additional burst of thrombin generation.

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The current clinical experience regarding the use of rFVIIa for the treatment of bleeding in patients with congenital or acquired platelet disorders is analysed briefly in this review.

rFVIIa in congenital platelet disorders

rFVIIa is being increasingly used in certain disorders of platelet dysfunction, particularly Glanzmann's thrombasthenia, which is a rare autosomal recessive inherited platelet disorder characterised by impaired platelet aggregation and due to defects in the platelet membrane glycoprotein (GP) IIb-IIIa. Bleeding manifestations, which usually appear in early childhood, range from easy bruising, purpura, epistaxis, gingival bleeds, haematuria, haemarthrosis, muscle haematomas to central nervous system bleed. When bleeding does not respond to local measures and/or antifibrinolytic drugs, platelet transfusion is currently the standard treatment. However, repeated platelet transfusions may result in GP IIb-IIIa and/or HLA immunisation and the development of refractoriness to platelets[10]. Tengborn and Petruson[11] first reported the successful use of rFVIIa (110 μg/kg) in the management of intractable epistaxis in a 2-year old child with Glanzmann's thrombasthenia. Following this report, several other authors substantiated the efficacy of rFVIIa in the management of bleeding or surgical procedures, using doses ranging from 120 to 300 μg/kg[12-22]. Poon and colleagues[13] successfully used rFVIIa to treat 24 bleeding episodes and to prevent bleeding during surgery in four children with Glanzmann's thrombasthenia, administering 89 to 116 μg/kg every 2 hours in association with antifibrinolytic drugs. On behalf of the International Data Collection on rFVIIa and Congenital Platelet Disorders Study Group, the same authors analysed the use of rFVIIa during 34 surgical/invasive procedures and 108 bleeding episodes in 59 patients with Glanzmann's thrombasthenia, including 29 with platelet antibodies. rFVIIa was effective in stopping bleeding in 29 of 31 (94%) evaluable procedures and in 77 of 103 (75%) evaluable bleeding episodes. There was one failure in a minor surgical procedure and another in a major surgical procedure, and 8 recurrences and 26 failures in bleeding episodes. Among the successful treatments, the median doses of rFVIIa as a bolus were 74-150 μg/kg (1-33 injections) in 23 surgical procedures and 28-238 μg/kg (1-48 injections) in 68 bleeding episodes; continuous infusions of rFVIIa were used in the remaining successful treatments. Two serious adverse events were reported –one was a deep vein thrombosis with pulmonary embolism, and the other was development of a thrombus in a ureter[16]. Based on the positive results, the authors concluded that rFVIIa seems to be a valid alternative to platelet transfusion in patients with Glanzmann's thrombasthenia, especially in those refractory to platelet transfusions. Chuansumrit and colleagues[19] reported on two children with Glanzmann's thromboasthenia undergoing invasive dental procedures. rFVIIa at a dose of 180-200 μg/kg, along with local measures including fibrin glue and mouth rinses with tranexamic acid, was successful in both cases. d'Oiron and colleagues[21] reported on the use of rFVIIa (an initial bolus dose of 70-110 μg/kg followed by a continuous infusion at a rate of 9-20 μg/kg/hour for 3-15 days) in three patients with Glanzmann's thrombasthenia undergoing invasive procedures. The treatment resulted in excellent clinical efficacy and tolerance in two cases, while in the third patient bleeding persisted for 10 days and was complicated by a thromboembolic event occurring 5 days after discontinuation of the drug. Valentino described four children with Glanzmann's thrombasthenia in whom surgical or traumatic bleeding was successfully prevented or controlled by rFVIIa[22]. In contrast to the above reports of success, Almeida and colleagues[20] found that rFVIIa was less satisfactory in the management of 33 episodes (28 acute bleeds and 5 surgical interventions) in seven children with inherited platelet function disorders (5 Glanzmann's thrombasthenia, 1 Bernand-Soulier syndrome and 1 storage pool disease). Most of the children received three doses of 100 μg/kg of rFVIIa at 90-minute intervals and tranexamic acid. While the patients with Bernand-Soulier syndrome and storage pool disease responded well to the rFVIIa therapy, children with Glanzmann's thrombasthenia had variable results with an excellent or good response during surgery or when the severity of bleeding was mild and a poor or ineffective response in severe bleeding episodes.

Similarly Peters and colleagues[23] reported on a 5-year-old boy with Bernand-Soulier syndrome and severe epistaxis who was not responsive to standard therapy but was successfully treated with rFVIIa. Finally, a patient with platelet-type von Willebrand's disease was reported to have been treated effectively with rFVIIa[24].

Based on the evidence from the literature, rFVIIa is currently approved in Europe for prophylaxis and treatment of bleeding in patients with Glanzmann's thrombasthenia with antibodies to GP IIb-IIIa and/or HLA, and past or present refractoriness to platelet transfusion. The recommended dose is a bolus injection of 90 μg/kg at 2 hour intervals for a minimum of three doses.

rFVIIa in acquired platelet bleeding disorders

The are a few reports describing the haemostatic effects of rFVIIa in thrombocytopenic patients[25,26]. One report[27] presented the case of an 8-year old girl with idiopathic thrombocytopenic purpura whose refractory epistaxis was successfully on two occasions with rFVIIa (at a dose of 85 μg/kg). Wrobel and colleagues[28] reported the cases of two patients with refractory chronic idiopathic thrombocytopenic purpura who underwent splenectomy and were prepared for surgery with a regimen including rFVIIa. The largest case series was published by Kristensen and colleagues[29] who studied 74 patients with moderate to severe thrombocytopenia due to impaired platelet production or immune destruction to evaluate the effect of rFVIIa administration. Given at a dose of 50 or 100 μg/kg, rFVIIa shortened the Ivy bleeding time in approximately 50 percent of the patients and all the eight patients with overt bleeding had a clinical benefit from rFVIIa administration.

rFVIIa has also been successfully used in oncohaematolgical patients with thrombocytopenia following chemotherapy associated or not with stem cell transplantation and severe bleeding refractory to standard haematological or haemostatic support[30-37]. Blatt and colleagues[30] used rFVIIa (boluses of 90-270 μg/kg with subsequent doses of 90 μg/kg every 4-24 hours for 3-14 days) for the treatment of severe haemorrhage in three transplanted patients; two of them had transient clinical responses. De Fabritiis and colleagues[31] reported on the use of rFVIIa for the treatment of severe bleeding episodes in seven patients with haematological malignancies and thrombocytopenia following chemotherapy: two had complete responses, three had partial responses and treatment failed in the other two patients. Hicks and colleagues[32] documented the efficacy of rFVIIa for the treatment of diffuse alveolar haemorrhage following bone marrow transplantation. Vidarsson and Onudarson[33] described a 27-year-old woman with acute myelogenous leukaemia and refractory thrombocytopenia, who developed a subdural haematoma, haemoptysis, and periorbital haematoma. rFVIIa (90 μg/kg) was administered every 2 hours for five doses, then every 4 hours for six doses. A rapid clinical improvement was noted, despite persistent thrombocytopenia.

Another report[34] described two patients with severe thrombocytopenia and life-threatening haemorrhage. A 75-year-old man with Waldenstrom's macroglobulinaemia and refractory thrombocytopenia presented with persistent epistaxis, which was unresponsive to platelet transfusion therapy. A single dose of rFVIIa (90 μg/kg) resulted in immediate cessation of haemorrhage. The second case, a 52-year old woman with acute lymphoblastic leukaemia, presented with severe thrombocytopenia and gastrointestinal bleeding unresponsive to platelet therapy. A single bolus dose of rFVIIa (90 μg/kg) substantially reduced the haemorrhage. The largest case series so far is that recently reported by Brenner and colleagues[35]. The authors, using an Internet-based registry, collected 24 cases in which rFVIIa was used in the management of haemorrhage in patients with thrombocytopenia associated with haematological malignancies. Patients received a median dose of rFVIIa of 85 μg/kg (range, 18-1040 μg/kg) and a median number of 1.6 doses (range, 1-8). Bleeding stopped in 11 of 24 patients (46%), markedly decreased in 8 of 24 patients (33%) and decreased in 4 of 24 patients (17%). In most patients, the response was achieved within 2.5 hours of administration of rFVIIa. On the basis of these results, the authors suggested that rFVIIa has a beneficial effect in this clinical setting. However, a case of ischaemic stroke, possibly related to the use of rFVIIa, was documented. Another severe rFVIIa-related adverse reaction was described by Mantzios and colleagues[36], who reported massive pulmonary embolism after treatment with rFVIIa in a thrombocytopenic patient with acute myeloid leukaemia and refractory bleeding.

rFVIIa has also been used successfully in uraemic patients, who may develop a bleeding disorder as a consequence of an acquired defect in platelet function[38,39].

Finally, rFVIIa use has been described in iatrogenic platelet disorders due to aspirin, clopidogrel and GP IIb/IIIa inhibitors in patients with cardiovascular disorders[40].

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Conclusions

The mechanisms of action of rFVIIa support its potential utility in bleeding conditions other than haemophilia characterised by impaired thrombin generation, such as quantitative and qualitative platelet deficiencies. However, while the data in the literature suggest that rFVIIa may be an alternative option to platelet transfusion in patients with Glanzmann's thrombasthenia, the published experience with rFVIIa in controlling bleeding in thrombocytopenic patients is too limited to draw any conclusions. Clinical trials are, therefore, needed to assess the safety and cost-effectiveness of this expensive approach in inherited and acquired platelet disorders.

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