Treatment of a Patient with Bernard-Soulier Syndrome and Recurrent Nosebleeds with Recombinant Factor VIIa

Dear Sir,

Bernard-Soulier syndrome (BSS) is a rare congenital bleeding disorder characterised by a prolonged bleeding time, large platelets and thrombocytopenia. Aggregation of BSS platelets is normal in response to ADP, epinephrine, collagen and arachidonic acid but there is no agglutination in response to ristocetin (1). The disorder is due to absence or abnormality of the platelet membrane glycoprotein complex Ib-IX-V (GP Ib), the receptor for von Willebrand factor (vWF). BSS-patients present with clinical symptoms as severe cutaneous and mucosal bleeding as well as bleeding from visceral sources.

Therapy for BSS-patients during hemorrhage presents a major challenge. Theoretically, platelet transfusions are the treatment of choice, but allo-immunization frequently occurs after repeated transfusions, in particular in complete GP Ib deficiencies. Other treatment modalities such as corticosteroids, splenectomy and desmopressin acetate (DDAVP) have been employed with minimal success (2). Here, we describe the first patient with BSS successfully treated with recombinant factor VIIa (rVIIa, NovoSeven®, Novo Nordisk).

The patient is a boy, born in December 1992, from non-consanguineous Hindustani parents. From the age of 3 months, he suffered from repeated nosebleeds which increased in frequency and severity after the age of 12 months. Blood testing showed thrombocytopenia (40-60 x 10⁹/l) and giant platelets (mean platelet volume 13,1 fI) in his blood smear. His bleeding time was >20 min, and he had a normal plasma factor VIII:vWF antigen level. Flow cytometry, utilising antibodies against GP Ib-α (CD 42-β) and IIIa (CD 61), revealed a complete deficiency of GP Ib-α.

In September 1995, he was admitted to the Pediatric Intensive Care Unit of our hospital in hypovolemic shock, due to a severe nosebleed and massive gastro-intestinal bleeding causing his hemoglobin (Hb) level to drop to 2 mmoll within several hours. Bleeding was arrested by transfusion of erythrocytes and platelet concentrate from 5 random donors. In the following years, his main clinical problem remained repeated nosebleeds which could be treated, mostly at home, with tranexamic acid, Spongostan and xylometazoline 0,5‰. DDAVP appeared not to be beneficial.

On May 17, 1997, he was admitted again to our hospital with a severe nosebleed which caused his Hb level to drop to 3,4 mmoll. During admission, he received erythrocyte transfusions on two different occasions. He was treated with tranexamic acid and use of tampons but this regimen appeared unsuccessful in arresting the bleeding. In light of the relative restraint on platelet administration in his case, he was treated with rVIIa (77 µg/kg), every 4 h during 24 h. Upon administration of rVIIa, his nosebleed stopped promptly and permanently and the boy was discharged in good condition on May 30.

The mechanism behind the clinical efficacy of rFVIIa in BSS remains to be fully elucidated but several intriguing possibilities are apparent. Previous studies demonstrated that GP Ib is required to reduce the velocity of blood platelets contacting the surface by prolonging the time available for occurrence of other interactions (3). Among these interactions is binding of GP Ib-IIIa (integrin α²β₃) to fibrinogen (Fg) and vWF to make the platelet-surface interaction irreversible. Administration of rVIIa to BSS patients induces enhanced thrombin formation at the site of the wound and, thrombin, in its term, displays two separate activities that could potentially act to compensate for the lack of GP Ib on the platelet membrane.

First, enhanced thrombin formation induces extra fibrin formation at the site of the wound which could act as a substrate for GP Ib-IIIa to facilitate binding of platelets through Ib-IIIa-Fg complex formation. In addition, increased activation of GP Ib-IIIa of already attached platelets by enhanced levels of thrombin may lead to a more rapid growth of the thrombus by facilitating platelet-platelet interaction. Hence, increased levels of thrombin at the site of the wound may induce clinically effective levels of irreversible platelet binding to the vessel wall and subsequent thrombus growth in spite of the short initial interaction time between platelets and the vessel wall. It is of interest to note that, in vitro, BSS platelets possess a greater capacity than normal platelets to generate thrombin, probably due to increased exposure of phosphatidyserine at their surface (4).

Our results suggest that rVIIa may be a valuable alternative for treatment of hemorrhages of BSS patients. This is of particular importance in light of the limited efficacy of DDAVP and restraints of platelet transfusions in complete GP Ib deficiencies, like our patient, where repeated administration of platelets may induce allo-immunisation leading to a refractory state.

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References

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