Pyelolithotomy in a patient with Glanzmann thrombasthenia and antiglycoprotein IIb/IIIa antibodies: the shortest possible duration of treatment with recombinant activated factor VII and platelet transfusions

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SUMMARY: Devecioğlu Ö, Ünüvar A, Anak S, Bilge İ, Ander H, Ziylan O. Pyelolithotomy in a patient with Glanzmann thrombasthenia and antiglyloprotein IIb/IIIa antibodies: the shortest possible duration of treatment with recombinant activated factor VII and platelet transfusions. Turk J Pediatr 2003; 45: 64-66.

Transfusion of platelet concentrates remains the first-line therapy for Glanzmann thrombasthenia in case of bleeding or preparation for surgery. However, development of antibodies to platelet glycoprotein (Gp) IIb/IIIa complex or human leukocyte antigens (HLA) is frequent and the main cause of platelet refractoriness. Recombinant activated factor VII (rFVIIa) is a potent alternative for patients with Glanzmann thrombasthenia with anti-platelet antibodies.

We describe a case of Glanzmann thrombasthenia with alloantibodies to platelet Gp IIb/IIIa complex who underwent a successful pyelolithotomy operation under the coverage of recombinant activated factor VIIa and platelet transfusions.

Key words: Glanzmann thrombasthenia, alloimmunization, hematuria, rVIIa, platelet, surgery.

Glanzmann thrombasthenia is a platelet function disorder due to the absence or abnormality of the platelet membrane glycoprotein (Gp) IIb/IIIa complex. Transfusion of platelet concentrates is a first-line therapy. However, development of alloantibodies to Gp IIb/IIIa complex is a major problem after repeated transfusions. In this case, different treatment modalities such as desmopressin acetate (DDAVP), corticosteroids, etc. have been used with minimal success. After the first successful use of recombinant activated factor VIIa [rFVIIa, NovoSeven® (Novo Nordisk, Bagsvaerd, Denmark)] by Tengborn and Petruson [1], it has been administered as a continuous or a bolus infusion for surgery in patients with Glanzmann thrombasthenia wo also had antibodies to Gp IIb/IIIa complex or human leukocyte antigens (HLA) or in patients without alloimmunization[2-4].

We report a patient with Glanzmann thrombasthenia wo also had alloantibodies to Gp IIb/IIIa complex who was successfully blocked with rFVIIa during pyelolithotomy operation, with ony three days' bolus infusion regimen, and also platelet transfusions. Considering the shortest possible time for a major surgery in patients with Glanzmann thrombasthenia, we gave platelet concentrates two hours before pyelolithotony and at the end of the operation.

Case Report

The patient was a nine-year-old boy diagnosed as Glanzmann thrombasthenia at five years of age. He was born to second-degree consanguineous parents with a family history of a brother who had expired from hypovolemic shock due to hematuria. He was lost to follow-up for about two years. In February 1998, he was admitted to the hospital with hypovolemic shock due to severe hematuria. He recovered by erythrocyte and platelet transfusions, and macroscopic hematuria stopped. Evaluation of hematuria revealed a stone in the pelvis of his left kidney. After he was discharged, he was followed from the outpatient

clinic. During this period, hematuria persisted, but hemoglobin levels were maintained with iron supplementation. However, a gross hematuria occurred five months later and transfusion of platelet concentrates was given again.

After this event, pyelolithotomy was planned, but transfusion of platelet concentrates did not shorten the bleeding time because of alloimmunization just before the surgery. Antibodies to Gp IIb/IIIa complex were detected for the first time using flow-cytometry analysis. Recombinant FVIIa was not commercially available in Turkey, and the surgery was cancelled. The patient was followed very closely for hydronephrosis. In October 1999, the size of the kidney stone became bigger and grade II hydronephrosis was detected. Antibodies to Gp IIb/IIIa were assessed again, and they were strongly positive. Surgery was planned with rFVIIa as it was available. Prior to initiation of treatment with rFVIIa, the patient and his parents were fully informed about the durg, and his father and mother signed an informed consent form. Recombinant FVIIa was given in a dose of 100 µg/kg (totally 2.4 mg) intravenously. Bleeding time performed two hours later was more than 15 minutes. A second dose of rFVIIa and 8 units of platelet concentrates were administered at the same time, although we had experienced refractoriness to previous applications. The next bleeding time, performed two hour later, was 5 minutes. After giving the third dose of rFVIIa, the operation began. During surgery, there was no significant bleeding. However, at the end of the operation, because of mild oozing from the operation site, 8 units of platelet concentrates were given, again. Recombinant FVIIa therapy was continued at the same dose for a total of 12 doses on the first post-operative day. On the second day, rFVIIa was given every 3 hours, and on the third day every 4 hours. After a total of doses, rFVIIa was stopped. At the post-op 40th hour, macroscopic hematuria ceased, and on the sixth day, microscopic hematuria also disappeared. The duration of macroscopic and microscopic hematuria after the pyelolithotomy was similar in patients without hemostatic defect. The patient was followed closely by hematological parameters that are given in Table I. The shortening of prothrombin time (PT) was observed on the first day of the operation (Day 0), and the other tests remained unchanged during the post-op period except for a mild increase in platelet count. PT returned to normal level after the third day. Bleeding time was normal by the seventh day, four days after the cessation of rFVIIa.

Discussion

Refractoriness due to alloimmunization is a common problem after repeated administration of platelet concentrates. Patients with Glanzmann thrombasthenia and antibodies to Gp IIb/IIIa complex have had problem during serious bleeding episodes or surgery. For a long time, they had been treated with alternative measures such as intravenous immunoglobulin (IVIG), DDAVP, steroids, etc. Recombinant FVIIa has been successfully used for hemophiliac patients with inhibitors to factor VIII or IX[5,6]. As in the case of use of rFVIIa, hemostasis is started by the formation of a complex between tissue factor and activated factor VII following trauma or injury. It has been shown that rFVIIa can induce hemostasis in the absence of FVIII and FIX. In addition, in vitro studies have shown that rFVIIa can bind to the activated platelet surface with low affinity and induce the thrombin burst for

Table I. Some Hematological Parameters of the Case (Pre- and Post-Operatively)

	-1	Operation (Day 0)	1	2	3	4	5	6	7
Hb (g/dl)	11.0	10.2	10.4	11.0	10.8	10.8	10.9	10.2	10.1
WBC (/mm^3)	5000	9400	6100	5700	–	–	3500	3300	3400
PLT (/mm^3)	320.000	403.000	416.000	430.000	–	–	340.000	284.000	267.000
BT (minutes)	>15	2	2	2	2	2	2.5	2.5	>15
PT (seconds)	14	7.4	7.6	8.0	13.4	17.2	14.4	–	12.9
aPTT (seconds)	33.1	31.1	28.4	27.6	32	30.9	31.4	–	24

BT : bleeding time.
PT : prothrombin time.
aPTT : activated partial thromboplastin time.

hemostasis[7]. Tengborn and Petruson[1] first reported the successful use of rFVIIa for severe epistaxis in a patient with Glanzmann thrombasthenia. After this report, rFVIIa was used by other investigators for bleeding episodes or surgery in patients with Glanzmann thrombasthenia with or without alloantibodies to platelet Gp IIb/IIIa complex or HLA[2-4,8]. It has also been used for patients with other congenital or acquired functional platelet disorders including Bernard-Soulier syndrome, platelet type (pseudo) von Willebrand disease, and thrombocytopathies due to uremia or myelodysplastic syndrome[9-12].

Recombinant FVIIa has been used as a continuous infusion for surgery in patients with Glanzman thrombasthenia who also had alloantibodies to platelet Gp IIb/IIIa complex or HLA for four procedures and as a bolus injection during bilateral herniorrhaphy in children with Glanzmann thrombasthenia without antibodies[2-4]. Three of them were minor procedures such as bilateral herniorrhaphy, central line removal and intestinal polypectomy and biopsy[2,3]. The other two were major procedures, one of them intestinal resection and the other Bilroth-2 gastrectomy[3,4]. Recombinant FVIIa was given for 1, 3, and 7 days in minor procedures, for 5 days in Bilroth-II gastrectomy, and for 15 days in intestinal resection. However, bilateral deep venous thrombosis and pulmonary embolism developed six days later after the cessation of rFVIIa in the last patient. In our patient, rFVIIa was used only for three days in conjunction with two platelet transfusions, one just before surgery and one immediately after. This is the shortest time reported for a major surgery in patients with Glanzmann thrombasthenia. The other difference was the use of rFVIIa as a bolus infusion instead of a continuous one for a major surgery.

Our experience supports that rFVIIa is effective and safe for patients with Glanzmann thnrombasthenia and alloantibodies to Gp IIb/IIIa complex. Bolus infusion can be given instead of continuous infusion with careful monitoring of bleeding. Combined rFVIIa treatment and limited platelet transfusion for three days may be sufficient instead of a long duration treatment. It is possible that the platelets bound all antibodies, and some residual platelets provide hemostasis.

In conclusion, the experience with rFVIIa for patients with Glanzmann thrombasthenia is still very limited due to the number of patients, bleeding episodes and surgical interventions. Accumulation of enough data will allow us to understand the role of rFVIIa in Glanzmann thrombasthenia. Better programs for the application of rFVIIa could be considered for the future.

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REFERENCES

1. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa (Letter). Thromb Haemost 1996; 75: 981.
2. Poon M-C, d'Orion R and the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. Recombinant activated factor VII (NovoSeven®) treatment of platelet-related bleeding disorders. Blood Coagul Fibrinolysis 2000; 11 (Suppl): 55-68.
3. d'Orion R, Menart C, Trzeciak MC, et al. Use of recombinant factor VIIa in 3 patients with inherited type 1 Glanzmann's thrombasthenia undergoing invasive procedures. Thromb Haemost 2000; 83: 644-647.
4. Wielenga JJ, Siebel Y, van Buuren HR, et al. Use of recombinant factor VIIa and HLA matched platelets to prevent bleeding during and after major surgery in a patient with Glanzmann's thrombasthenia (Abstract). Haemophilia 1998; 4: 299.
5. Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. Blood Coagul Fibrinolysis 1998; 9 (Suppl): 119-128.
6. Kessler CM. New products for managing inhibitors to coagulation factors: a focus on recombinant factor VIIa concentrate. Curr Opin Hematol 2000; 7: 408-413.
7. Hedner U. NovoSeen as a universal haemostatic agent. Blood Coagul Fibrinolysis 2000; 11 (Suppl): 107-111.
8. Poon M-C, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. Blood 1999; 94: 3951-3953.
9. Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa (Letter). Thromb Haemost 1998; 80: 352.
10. Fressinaud E, Sigaud-Fix M, Le Boterff C, Piot B. Use of recombinant factor VIIa (NovoSeven®) for dental extraction in a patient affected by platelet-type (pseudo-) von Willebrand disease (Abstract). Haemophilia 1998; 4: 299.
11. Révész T, Arets B, Bierings M, van den Bos C, Duval E. Recombinant factor VIIa in severe uremic bleeding (Letter). Thromb Haemost 1998; 80: 353.
12. Meijer K, Sieders E, Slooff MJ, de WolfJTh, van der Meer J. Effective treatment of severe bleeding due to acquired thrombocytopathia by single dose administration of activated recombinant factor VII (Letter). Thromb Haemost 1998; 80: 204.