

Weekly low-dose recombinant factor VIIa prophylaxis in Glanzmann thrombasthenia

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Glanzmann thrombasthenia is an inherited disease causing bleeding episodes due to platelet dysfunction. The standard treatment for moderate-severe bleeding is platelet transfusion. Recombinant factor VIIa (rFVIIa) is successfully used in bleeding episodes and invasive procedures. Here, we present a patient with Glanzmann thrombasthenia, whose bleeding episodes could only be controlled by rFVIIa. The patient is a 28 years old male, who has had frequent bleeding episodes unresponsive to local hemostatic agents and tranexamic acid and had an anaphylactoid reaction to platelet transfusion. We started the patient on a low-dose (20 µg/kg) rFVIIa once a week. The patient has no spontaneous bleeding since then. This is the first case report of a Glanzmann thrombasthenia patient on routine prophylaxis with low-dose rFVIIa. *Blood Coagul Fibrinolysis*

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Introduction

Glanzmann thrombasthenia, is an autosomal recessive inherited disease. Platelet dysfunction in Glanzmann thrombasthenia results from a quantitative or qualitative disorder of the platelet membrane glycoprotein IIb/IIIa (integrin α IIb β 3) complex [1]. α IIb β 3 is a heterodimeric molecular complex that is triggered by physiological agonists and serves as a fibrinogen receptor that is important in platelet aggregation induced for fibrin clot retraction. According to the differences in glycoprotein IIb/IIIa levels, three Glanzmann thrombasthenia classifications have been determined; in type I, glycoprotein IIb/IIIa levels are less than 5%, in type II, glycoprotein IIb/IIIa levels are between 5 and 20% and in type III there is a qualitative defect in the glycoprotein IIb/IIIa function [2].

Bleeding episodes are typically mucocutaneous. Less frequent bleeding sites, like cerebral and intra-articular may also be seen [3]. Bleeding complications are common after trauma and surgical procedures like tooth extraction [4].

Light transmission aggregometry is a diagnostic tool to evaluate the platelet function. This test is quite specific for Glanzmann thrombasthenia because platelet aggregation cannot occur with any agonist except ristocetin [5]. In flow cytometry analysis, the levels of CD41 and CD61 are significantly reduced or absent, indicating nonfunctional α IIb β 3. The levels of CD42 are normal [3].

Treatment measures for mild hemorrhage include the use of local hemostatic and antifibrinolytic agents, such as nasal plugs with gelatin sponge, fibrin glue, and topical thrombin. The standard treatment for severe hemorrhage

is platelet transfusion. Moreover, repeated transfusions may lead to the development of antibodies against glycoprotein IIb/IIIa and/or human leukocyte antigens, resulting in anaphylaxis and/or platelet transfusion resistance. In addition, transfusions are not always easily available and the use of blood products is related to the risk of infection and allergic reaction [6,7].

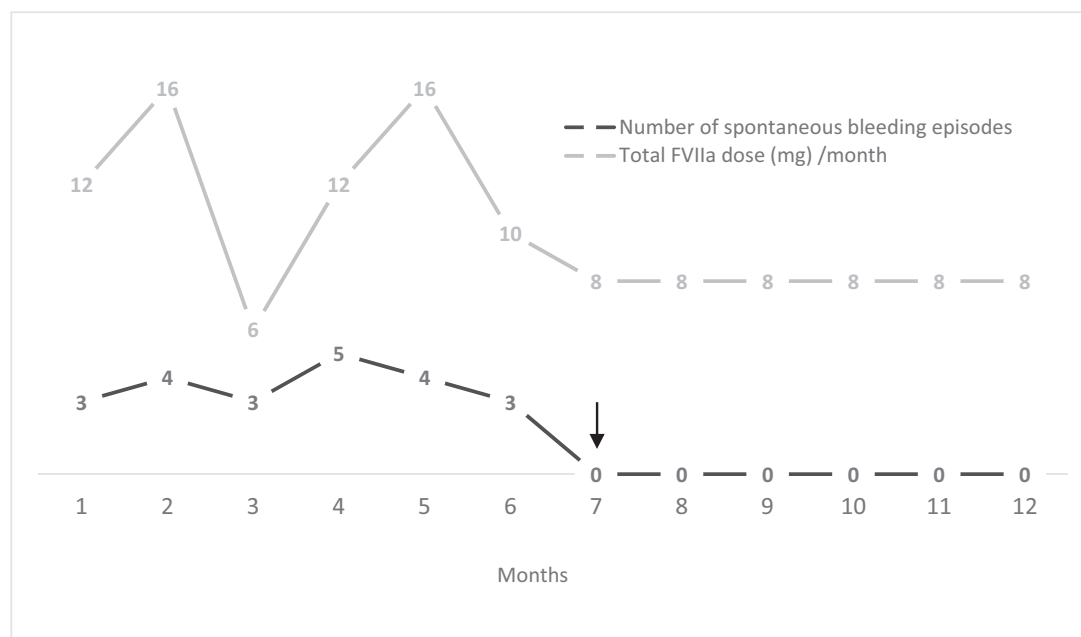
Recombinant factor VIIa (rFVIIa) is thought to bind weakly to the surface of the platelets through a mechanism independent of the tissue factor and increases thrombin formation by enhancing the activation of factors IX and X. The increased amount of thrombin augments the platelet adhesion and the platelet aggregation including platelets without glycoprotein IIb/IIIa [8]. This activation of platelets improves the fibrin clot structure in patients with Glanzmann thrombasthenia and improves hemostasis by reducing the clot transmission and tightening the fibrin network [9,10].

Here, we present a patient with Glanzmann thrombasthenia, whose bleeding episodes could be controlled by prophylaxis with low-dose rFVIIa.

Case report

A 28-year-old male patient was diagnosed with Glanzmann's thrombasthenia at the age of 1 year old. The tests performed in our center were also consistent with Glanzmann's thrombasthenia. Since the CD41 was negative, we diagnosed the patient as type I Glanzmann thrombasthenia. He had a history of many long-term ICU admissions due to gastrointestinal bleeding and cranial bleeding. He suffered from nosebleeds, gum bleeds, and

Fig. 1



Monthly doses and bleeding episodes before and after the initiation of recombinant factor VIIa prophylaxis. Arrow indicates the first month of the prophylactic regimen.

spontaneous ecchymosis three to four times a week. He has epilepsy. Epileptic episodes continued despite appropriate treatment. Traumatic hemorrhages were seen during the epileptic episodes due to uncontrolled falling. Bleeding episodes were unresponsive to tranexamic acid. He had a history of anaphylactic shock with platelet transfusion. Bleeding episodes could only be controlled by the use of rFVIIa. He had received two to three doses of rFVIIa once every 2 weeks in the last 6 months before admission, mostly for mucocutaneous bleeds. Doses were between 20 and 70 $\mu\text{g/kg}$ range. His mucocutaneous bleeds were controlled by one or two doses of 20–30 $\mu\text{g/kg}$ rFVIIa given 2–4 h apart. For traumatic bleeds, he received two to three doses of rFVIIa 50–70 $\mu\text{g/kg}$. He didn't need any blood transfusion since his last gastrointestinal bleed which was 8 years ago. But he had iron deficiency anemia with a hemoglobin level of 11 g/dl. Due to bleeding episodes, he had to take many sick leaves and was about to lose his job. Prophylaxis with rFVIIa was started in January 2018 as 20 $\mu\text{g/kg}$ /dose/once a week by obtaining off-label approval from the Turkish Ministry of Health.

The patient had no spontaneous bleeding after the start of the prophylactic regimen. His iron deficiency was resolved. Since the patient was doing very well on prophylaxis, we didn't perform any clotting test to measure the effectiveness of the treatment. He had to have a tooth

extraction during prophylaxis and we planned 20 $\mu\text{g/kg}$ rFVIIa dose just before and 2 h after the procedure. But this dose was not enough. He admitted to the emergency department 8 h after the dental procedure, oozing blood from the wound. We had to give him two doses of 70 $\mu\text{g/kg}$ rFVIIa, 2 h apart, to stop the bleed. A minor trauma of the first finger was successfully treated with a single dose of 50 $\mu\text{g/kg}$ rFVIIa. He did not experience any thrombotic events. A scheme of the doses and bleeding episodes can be seen in Fig. 1.

Discussion

rFVIIa is known to be effective in treating bleeding episodes in Glanzmann thrombasthenia. Based on the case reports and case series response to treatment varies between 65 and 95% [11–13]. It is more effective when used before an invasive procedure rather than used after the bleeding starts [5]. rFVIIa treatment should be initiated as soon as bleeding begins (83% success within 6 h). For moderate and severe bleeding, approximately 90 $\mu\text{g/kg}$ bolus injection, once every 2 h, is recommended until bleeding stops [13]. Prophylaxis is a standard of care in hemophilia A and B patients. rFVIIa is used in congenital and acquired hemophilia with inhibitors. Although everyday usage of 80–90 $\mu\text{g/kg}$ is recommended for prophylaxis in these patients, less frequent injections and lower doses are known to be effective. In congenital FVII deficiency, 20 $\mu\text{g/kg}$ doses are used to treat bleeding episodes.

Prophylaxis with rFVIIa is rarely needed in FVII deficiency. In one very recent study, Levy-Mendelovich *et al.* showed that very low concentrations of FVIIa can induce thrombin generation in Glanzmann thrombasthenia patients [14]. According to this article, the lowest dose of FVIIa that can improve thrombin function was equivalent to 25 µg/kg. There is no information in the literature about regular prophylactic usage of rFVIIa in Glanzmann thrombasthenia. We concluded the information above and decided to start from the lowest and least frequent dose of rFVIIa. We planned to increase the dose and frequency as the patient needed but no such thing was necessary since the patient had no spontaneous bleeding. The patient's quality of life increased dramatically. Considering all costs (hospital admissions, rFVIIa, days off work) rFVIIa prophylaxis was a cost-effective option. Given the short half-life of FVII, it is hard to explain how a weekly dose can prevent bleeding in Glanzmann thrombasthenia. We can extrapolate our experience from hemophilia A patients with inhibitors: every other day or three times a week rFVIIa is often enough for prophylactic treatment of these patients. Enhanced thrombin production with FVIIa, probably acts beyond the half-life of the product. Ex-vivo studies show residual thrombin generating capacity and increased firmness of clot after FVIIa injection [14,15]. This could be due to platelet microparticle release [16,17]. We expected to prevent bleeding after his tooth extraction with lower doses of FVIIa than we used before, but we had to give the usual high and frequent doses. Probably this residual thrombin activity was not enough for wider tissue defects. One of the main concerns about this treatment was the thromboembolic risk. In one study, two patients with Glanzmann thrombasthenia who received continuous, high-dose rFVIIa combined with antifibrinolytic therapy developed deep venous thrombosis with pulmonary embolism and ureteric clots [13]. Our patient is young and has no thromboembolic risk and the dose of rFVIIa is low so thrombi are unexpected. Low-dose weekly rFVIIa prophylaxis can be an option in Glanzmann thrombasthenia patients who have a high frequency of bleeding. To our knowledge, our patient is the only one reported in the literature. Safe dose and frequency can only be determined after the experience increases around the world.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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