Abstract: Glanzmann thrombasthenia (GT) is a rare autosomal recessive disorder characterized by a deficiency or functional defect of platelet glycoprotein (GP) IIb/IIIa. Physiologically, this platelet receptor mediates aggregation of activated platelets by binding the adhesive proteins, fibrinogen, von Willebrand factor (VWF) and fibronectin. This facilitates attachment and aggregation of platelets at sites of vascular injury. We reported the management of a pterional meningioma resection in a patient with Glanzmann thrombasthenia, with recombinant factor VIIa (rFVIIa - NovoSeven®) as haemostatic agent.

A 48-year-old woman suffering from Glanzmann thrombasthenia was scheduled for spheno-orbital meningioma en plaque surgery. Because of repeated platelet transfusions, this patient developed isoantibodies against missing GP IIbIIIa and alloantibodies against Human Leukocyte Antigen (HLA) leading to refractoriness to platelet transfusions. We observed that Novoseven© offered sufficient haemostasis conditions. Therefore, we noticed a deep vein thrombosis. This imposed us to use low weight molecular heparin despite recent surgery.

Key words: Glanzmann thrombasthenia; meningioma; bleeding; GPIIb/IIIa; recombinant activated factor VII; anti-platelet antibodies; platelet transfusion; inherited platelet disorders; treatment.

Case-report

A 48-year-old woman (62 kg) suffering from Glanzmann thrombasthenia was scheduled for sphen-orbital meningioma en plaque surgery (Fig. 1). This tumor with osseous involvement caused severe right exophthalmia. Because of repeated platelet transfusions, this patient developed isoaotibodies against missing GPIIbIIIa and alloantibodies against HLA leading to refractoriness to platelet transfusions with allergic symptoms (cutaneous rash). According to the blood haemostasis experts, recombinant factor VIIa represented an alternative treatment strategy.

The disease was discovered in the patient’s youth; she suffered from a complete lack of GPIIbIIIa. Platelet aggregation response to all physiological agonists was absent except to high doses ristocetin. The Collagen/Epinephrine and Collagen/ADP “closure time” where markedly increased (PFA-100® [Siemens, Munich, Germany]). She presented several episodes of severe gastric haemorrhage, with deep anaemia necessitating recently two admissions in intensive care unit. Bleeding control was achieved by endoscopy and haemostatic measures, including NovoSeven©. She had history of numerous persistent epistaxis and curettage due to gynaecologic haemorrhage.

INTRODUCTION

Glanzmann thrombasthenia (GT) is a rare autosomal recessive disorder characterized by a deficiency or functional defect of platelet glycoprotein (GP) IIb/IIIa (1). Physiologically, this platelet receptor mediates aggregation of activated platelets by binding the adhesive proteins, fibrinogen, von Willebrand factor (VWF) and fibronectin. This facilitates spreading and aggregation of platelets at sites of vascular injury. We reported the management of a pterional meningioma resection in a patient with Glanzmann thrombasthenia, with recombinant factor VIIa (rFVIIa - NovoSeven® [Novo Nordisk, Bagsvaerd, Denmark]) as haemostatic agent.
Pterional craniotomy and extradural resection of any infiltrated bone, the standard surgical approach for this localisation, was performed. The intracranial and orbital tumor was removed with reconstruction of the dura and the lateral bone.

General anesthesia was performed with continuous infusion of propofol and remifentanil. Orotracheal intubation was facilitated by cisatracurium. During surgery, normovolemia was achieved with cristalloids (Plasmalyte A® and saline 0.9%) and colloids infusions (Volulyte®). The patient was installed with two venous catheters placed in the right forearm and the right internal jugular vein. Repeated blood analyses were achieved through a radial arterial line. We used recombinant factor VIIa associated with tranexamic acid (Exacyl® [Sanofi-Aventis, Paris, France]) as shown in table I. Exacyl® was administered IV on the peripheral catheter and NovoSeven® on the central one.

During craniotomy and meningoia dissection, important bleeding justified double dose Novoseven® despite the patient remained hemodynamically stable. Repeated controls of haemoglobin showed a significant constant decrease as shown on figure 2. One red blood cell concentrate was transfused at the end of the surgery. On the third day post intervention, because of slight epistaxis, the NovoSeven® dose was doubled once again. No more transfusion was needed but the patient received iron (Venofer® [Fresenius, Hessen, Germany]) IV at J3, J5 and J7.

On day 8, the patient described a painful swelling on the right side of the neck. Doppler echography confirmed an internal jugular venous thrombosis nearby central venous line. Thus, the catheter was removed and enoxaparin subcutaneously was progressively introduced until 1 mg/kg/24 hours. Initial scheme of NovoSeven® was left unchanged. No more complication was observed until the end of the hospitalisation on day 14.

**DISCUSSION**

Glanzmann thrombasthenia (GT) is a rare autosomal recessive disorder characterized by a deficiency or functional defect of platelet GP IIb/IIIa. Patients with GT have normal platelet count and morphology, prolonged bleeding time and sometimes absent or decreased clot retraction. Diagnosis is usually performed from platelet aggregation studies (absent or markedly impaired platelet aggregation responses to all physiological agonists including ADP, collagen, epinephrine, thrombin and arachidonic acid except ristocetin) and from GP IIbIIIa analysis by flow cytometry (2). Common clinical expression is mucocutaneous bleeding (epistaxis, purplish-type bleeding, gum bleeding and menorrhagia) but postoperative or posttraumatic bleeding can be life-threatening. With local measures and antifibrinolytic drugs, platelet transfusions are the standard treatment of bleeding in GT. The fact that most patients receive red cell and/or platelet transfusions repeatedly makes the production of isoantibodies reactive with GP IIb/IIIa likely. Such antibodies are antigen-driven and may block platelet aggregation, as well as leading to the rapid removal of transfused platelets by

*Fig. 1. — Right spheno-orbital meningioma en plaque*

| Table I |
|------------------|---|---|---|---|---|---|---|---|
| rFVIIa (NovoSeven®) and tranexamic acid (Exacyl®) doses (6 mg is about 90 mcg/kg) | J-1 | J0-1 | J+2-3 | J+4-5 | J+6-7 | J+8-9 | J+10-11 |
| NovoSeven® | α | 6 mg q2h | 6 mg q3h | 6 mg q4h | 6 mg q6h | 6 mg q12h | 6 mg q24h |
| Exacyl® | 1 g q8h | 500 mg q8h | 500 mg q8h | 500 mg q8h | α | α | α |
immune mechanisms. These antibodies may cause patients to become refractory to further transfusions (3).

Recombinant factor VIIa (recombinant activated factor VII or eptacog alfa, NovoSeven®) is structurally similar to human plasma derived coagulation factor VIIa but is manufactured using DNA biotechnology. When complexed with tissue factor, it can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a haemostatic plug by converting fibrinogen to fibrin and thereby inducing local haemostasis. rFVIIa is approved in many countries as an intravenous hemostatic agent in patients with congenital haemophilia, acquired haemophilia, factor V deficiency and GT (4). Recommended dosage schedule for these indications are 90 mcg/kg each 2-3 hours (5, 6). The use of this drug may be limited because of the cost factor.

Others possibilities are activated prothrombin complex concentrate (aPCC) known as factor height bypassing activity (FEIBA) and platelet transfusions (7, 8).

In our case, rotational thromboelastometry (ROTEM©) was performed in order to evaluate efficiency of our treatment after 3 doses of rFVIIa. Unfortunately, it didn’t show a significant difference in comparison with the preoperative testing. This is in line with previous studies which confirmed that the ROTEM is not the method of choice to monitor rFVIIa therapy in Glanzmann patients (9).

The clinical haemostatic response to intravenous NovoSeven® was quite difficult to appreciate because of the haemorrhagic nature of the intervention. Despite of abundant losses, only one blood cell concentrate was needed at the end of the surgery and at no moment of the procedure, haemodynamic was compromised. We observed that Novoseven® offered sufficient haemostasis conditions.

Non-serious adverse events of rFVIIa include nausea, fever, injection-site pain, skin rash and increased value for ALT, alkaline phosphatase and lactate dehydrogenase. Serious events are thrombotic ones: myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation. They have generally occurred in patients with predisposing risk factors or for non-approved conditions. However, except neoplastic condition, our patient didn’t have any other risk factors and had an approved condition. The central venous thrombosis probably caused by the internal jugular catheter imposed us to use low weight molecular heparin despite recent surgery. Rare but with significant clinical relevance, these side effects have to be evoked before using NovoSeven©.

In conclusion, rFVIIa allowed us to realise safe neurosurgery by a patient with Glanzmann
thrombasthenia who had developed a platelet transfusion refractory state, induced by antiplatelet antibodies. The dose of NovoSeven® needed to control haemostasis was quite impressive and not well defined. More clinical trials are recommended to further assess the efficacy, the safety and optimal regimen of rFVIIa for surgical coverage in GT.

References