orphanaesthesia

Anaesthesia recommendations for

Glanzmann's thrombasthenia

Disease name: Glanzmann's thrombasthenia

ICD 10: D69.1
OMIM: 273800, 619267

Synonyms: Glanzmann syndrome; Glanzmann-Nägeli syndrome; Glycoprotein IIb (GPIIb/III) complex deficiency; Haemorrhagic thrombasthenia; Hereditary thrombasthenia; Hereditary thrombocytopenic purpura; Platelet Fibrinogen receptor deficiency; Platelet glycoprotein IIb/IIIa deficiency; Thrombasthenia; Thrombocytasthenia.

Disease summary: Glanzmann's thrombasthenia (GT) is an autosomal recessive platelet function disorder caused by mutations in the ITGA2B and ITGB3 genes (chromosome 17) encoding the αIIbβ3 integrin, leading to abnormality of the platelet membrane glycoprotein complex IIb/IIIa. Genetic mutations split equally between GPIIb and GPIIIa. Some cases are suspected to be transmitted as an autosomal dominant trait. Glycoproteins play a major role in platelet functioning, as it is part of the membrane receptors indispensable for platelet aggregation and interaction with fibrinogen.

This medical condition was first described in 1918 by Eduard Glanzmann (1887–1959) and Otto Nägeli (1871–1938).

In most patients, the diagnosis of GT is made in childhood, and in some cases shortly after birth, with the presence of purpura in places of pressure during natural childbirth. The laboratory criteria for diagnosis include normal platelet count and morphology, prolonged bleeding time, marked absence or decrease in platelet aggregation in response to ADP, collagen and epinephrine, but normal for ristocetin, and study of normal plasma coagulation. In the clinical presentation of the disease, haemorrhagic signs (particularly mucocutaneous) occur, such as purpura, gingival haemorrhage, menorrhagia and mainly epistaxis. The severity of the bleeding is variable. The most serious episodes are the result of trauma or exacerbation of physiological bleeding. Menarche represents a risky situation, the same occurring with pregnancy and childbirth of patients with the disease. Clinical manifestations tend to decrease with adulthood. GT is rare with low incidence rates among the general population (1:1,000,000), but it can become frequent in racial groups where consanguineous marriages occur.

The expression of GPIIb/IIIa on the platelet surface detected under flow cytometry determine three subtypes of GT. These are type I (GPIIb/IIIa 5 % or less), type II (GPIIb/IIIa 5–20 %) variant or type III (GPIIb/IIIa >20 % to normal, normal levels of integrin, but the protein is nonfunctional).

The standard treatment of haemorrhagic episodes and their prevention is platelet transfusion. This measure is generally effective, although alloimmunisation subsequently limits the average life of the infused platelets leading to platelet refractoriness. The alternative is recombinant activated factor VII (rFVIIa) currently approved in the EU for GT

patients with platelet antibodies and past or present history of refractoriness to platelet transfusion, or when platelets are not readily available.

An acquired form of GT is also seen which is caused by antibodies to platelet integrin αIIbβ3. These patients have low platelet count with a moderate-to-severe bleeding tendency, while some patients may have normal platelet counts. It is commonly found in association with autoimmune disorders, haematological malignancies, and infections. Acquired GT may also result from taking GPIIb/IIIa inhibitory medications (e.g. abciximab, eptifibatide, or tirofiban).

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

There is no typical surgery, but specific care in all patients undergoing anaesthesia with GT is necessary.

Type of anaesthesia

The surgeries in thrombasthenic patients, whose incidence is quite low, require perfect teamwork between the anesthesiologist, the surgeon and the haematologist so that the procedure can be planned and performed safely. The availability of blood and blood products should be guaranteed.

Regional anaesthesia should be avoided.

Necessary additional pre-operative testing (besides standard care)

Additional exams may be requested depending on the type and size of the surgery. Specifically, concerning GT, patients have a history of bleeding and transfusions, with prolonged bleeding time and normal platelet count.

For GT patients who previously had received platelet concentrates and/or red cell transfusion, it is also helpful to do studies on anti-platelet antibodies (anti-HLA, anti-GPIIbIIIa) particularly before major surgery, to give an idea whether they may be refractory to platelet therapy.

Because there is no universally available monitor of platelet function, its clinical course is difficult to monitor.

Peri-operative tests include measurement of closure times (PFA-100/200™), bleeding time, light transmission aggregometry (LTA), multiple electrode aggregometry (MEA), and thromboelastography (TEG). MEA and TEG are not widely available.

Particular preparation for airway management

In patients with haemorrhagic diathesis, surgical or invasive interventions should be performed with much more caution and care.

Anaesthesiologists and intensivists must be attentive during the peri-operative management of these patients, as laryngoscopy and intubation can cause persistent bleeding, making airway management difficult and even requiring intensive care.

Patients with TG often experience nasal bleeding, so the insertion of nasogastric tubes should be avoided. Uzunlar et al. reported the use of recombinant activated factor VII (rFVIIa) to interrupt a case of nasopharyngeal bleeding after passing a nasogastric tube.

Particular preparation for transfusion or administration of blood products

The peri-operative evaluation of the haematological state in these patients is mandatory.

These patients have conventionally been managed with blood and blood component (platelet-rich plasma and platelet concentrates) transfusions to control haemorrhage resulting from trauma or surgical procedures.

Assessing platelet antibody status before major surgery is of paramount importance. Indeed, not all patients with platelet antibodies will not respond to platelets, but some insights into platelet antibody status are important if a platelet transfusion is the only therapeutic modality available.

Patients with GT, particularly the type I patient with 5 % or less platelet surface GPIIb/IIIa, may develop platelet antibodies to GPIIb/IIIa protein (to any epitope of GPIIb/IIIa).

Any patient who receives a platelet or red blood cell transfusion may develop platelet antibodies against HLA antigens (human leukocyte antigen antibodies). Transfusion of leukocyte-depleted blood products decreases (but does not eliminate) the formation of HLA antibodies. The best strategy to decrease this probability is to use HLA-matched single-donor leukocyte-poor platelet concentrate – this is difficult to achieve in some scenarios.

The rFVIIa currently is approved in the EU for GT patients with platelet antibodies and past or present history of refractoriness to platelet transfusion, or when platelets are not readily available.

Particular preparation for anticoagulation

No recommendations reported.

Particular precautions for positioning, transportation and mobilisation

Patients should be handled with extreme care, both in positioning and in transport. They must be placed carefully on the operating table, the surface of which must be padded to reduce the risk of trauma. Some may develop purpura or ecchymosis under pressure in places of contact.

Interactions of chronic disease and anaesthesia medications

No specific interaction of GT with anaesthetic drugs. NSAIDs should be avoided.

Anaesthetic procedure

In patients with coagulopathies, the levels of catecholamines shouldn't be increased to the detriment of haemostasis, as well as the use of drugs that alter platelet function can cause haemorrhagic manifestations. The patient must receive strict monitoring of volume replacement, bleeding, temperature and electrolytes. Vascular accesses must be adequate for the size of the surgery.

A specialised assessment with haematology should be done.

Observed approaches are: transfusion of platelets in the peri-operative period and maintaining haemoglobin at 10 g/dl through transfusion of red blood cells. Although many patients receive transfusions at some point in their lives, most respond well to therapy.

Platelet transfusion remains the first-line therapy for GT in case of bleeding or prophylaxis for surgery unless there are antibodies to platelets. In thrombasthenic patients with antiplatelet antibodies, registries and case series suggest that rFVIIa is a potent alternative for treatment and prophylaxis of bleeding. At high concentration (from high dose), rFVIIa has been shown to bind to the platelet surface to directly activate factors IX and X independent of tissue factor, thus increasing the generation of thrombin. Increased thrombin generation can then provide a strong signal for recruiting other platelets.

Antifibrinolytic drugs, epsilon amino-caproic acid and tranexamic acid have been effective in controlling bleeding in thrombocytopenic patients; they can be used as an adjunctive therapy in thrombasthenia when treated with other primary haemostatic agents (e.g. platelets, rFVIIa). The effectiveness of using antifibrinolytic drugs alone in major surgery is uncertain.

The systematic use of epsilon amino-capróic acid before dental procedures has already been recommended. Desmopressin (1-deamino-8-D-arginine vasopressin) has been used in some patients without proven efficacy.

Menorrhagia cases are treated with high doses of estrogens conjugates administered intravenously for 24 to 48 hours, followed by a combination of estrogen and progesterone orally until the bleeding resolves. The patient must maintain the use of an oral contraceptive in normal doses indefinitely.

It was observed that the oral contraceptive based on norethisterone was effective in the treatment of gastrointestinal bleeding from telangiectasias in patients with GT.

The successful management of GT patients subjected to cardiopulmonary bypass requires proper application of a comprehensive transfusion protocol guided by TEG and MEA, to prevent excessive peri-operative bleeding. Prophylactic and therapeutic platelet transfusions are needed for surgery in GT patients as bleeding is unpredictable. Patients can be managed with single donor platelets with TEG guidance without the requirement of factor VIIa. Recombinant factor VIIa may be reserved for excessive post-operative bleeding in patients of GT who have developed antiplatelet antibodies. Topical application of gel foam soaked in thrombin, and prophylactic use of antifibrinolytic agents like tranexamic acid are additional measures to control bleeding. Repair of the valve when feasible instead of replacement is advisable in patients with GT because of the additional concern about bleeding when anticoagulation is required after valve replacement surgery. If valve replacement is required, then a bioprosthetic valve is to be preferred.

Particular or additional monitoring

GT is an uncommon condition and, as there is no universally available test for platelet function, its clinical course is difficult to monitor. Techniques include measurement of closure times (PFA-100/200™), bleeding time, MEA and TEG.

MEA is a test of platelet function in whole blood. The test can be used to diagnose platelet disorders, monitor antiplatelet therapy, and is also investigated as a potential predictor of

transfusion requirements and bleeding risk in surgery. The instrument detects a change in electrical impedance when platelets aggregate on metal electrodes in the test cuvette.

TEG technology measures viscoelastic and mechanical features of developing clot and can evaluate all phases of haemostatic efficacy using a single blood sample. In addition, the efficacy of the treatments can also be evaluated. Patients diagnosed with GT are at high risk for severe bleeding during and after surgical procedures. Necessary therapeutic options among thrombocyte replacement, rFVIIa, and antifibrinolytic therapies can be implemented during the peri-operative period taking the haematological features of patients and the surgical method into account and the results can be monitored via TEG when necessary. In addition, anaesthesiologists must be precise and kind during invasive procedures. TEG is used for the diagnosis of bleeding-coagulation disorders and in determining the efficacy of treatment by providing an evaluation of coagulation parameters in many aspects in a short time.

Possible complications

Post-operative bleeding can be critical, but when they are controlled and anaemia corrected, patients have a good prognosis.

Post-operative care

Depending on the magnitude of the intervention, it is recommended to remain in the ICU for 24 hours post-operatively, use a drain to quantify the bleeding and avoid the use of anti-inflammatories.

Disease-related acute problems and effect on anaesthesia and recovery

The biggest problem for thrombasthenia patients in the immediate post-operative period is bleeding, which may require intensive care and delay hospital discharge. An individualised and careful therapy, and the availability of blood and blood products, will reduce morbidity.

Ambulatory anaesthesia

After a thorough assessment of the case and the severity of the symptoms, diagnostic and minimally invasive procedures may be eligible for ambulatory anaesthesia.

Obstetrical anaesthesia

Pregnancy and childbirth are rare and associated with a high risk of severe bleeding, so the peripartum care of patients with GT should be multi-professional.

The mother needs to be assessed for platelet antibody status early and monitored during pregnancy, as these antibodies can cross the placenta, resulting in harm (thrombocytopenia, bleeding) to the foetus and neonate.

The normal foetal platelets may cause maternal sensitisation resulting in development of alloimmunisation, or may further increase the antiplatelet antibodies levels, the underlying mechanism being similar to Rh-isoimmunisation.

If a mother has GT, and if a father is heterozygous for GT, there will be a chance that the baby may have GT. Thus, genetic testing of the father in a high-risk population may be important and care for the newborn for potential GT is important (e.g., no invasive procedure including monitoring electrode insertion; need for atraumatic delivery with no vacuum, forceps, etc.).

Intravenous gamma-globulin therapy (IVIg) can be administered the night before surgery in an attempt to cushion an antiplatelet response.

Bell and Savidge report treatment of a patient with rFVIIa during two pregnancies and spinal surgery. A particular risk is a postpartum haemorrhage (PPH), reduced by modern obstetric practices and prolonged uterine contraction.

The caesarian section may reduce the risk of PPH possibly by more thorough uterine evacuation, but late PPH remains a risk until the placental site heals. Some institutions advocate the use of antifibrinolytics such as tranexamic acid for 14 days postpartum as a preventive measure for PPH. In this respect, rFVIIa has a good effect profile, the absence of platelet sensitisation and a rapid effect, and can be useful.

Other treatments described include the removal of antibodies by plasmapheresis and transfusion of platelets from a single donor and HLA compatible. This technique significantly decreases the antibody titer and allows for an efficient transfusion of compatible platelets. Good surgical haemostasis and oxytocin infusions are also an integral part of care.

Kashyap et al. reported the peri-operative management of a patient with thrombasthenia and alloimmunisation who developed secondary postpartum haemorrhage and was successfully treated with oral prednisolone.

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