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Case Report

Glanzmann's Thrombasthenia Proposed Optimal Management During Surgery and Delivery

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Summary: Glanzmann's thrombasthenia (GT) is an autosomal recessive disorder of platelet function. Conventional management is by platelet transfusion, given before invasive interventions. Alloimmunization resulting in platelet refractoriness and an unpredictable response to platelet infusion have provided particular management difficulties in the past. More recently recombinant (r)VIIa (Novoseven®) has a valuable role in the treatment of platelet function disorders. Treatment of a patient with GT during two pregnancies and spinal surgery is reported. An algorithm is presented to provide a structured and consistent approach to treatment.
Key Words: Thrombasthenia—Platelet refractoriness—Surgery—Pregnancy—rVIIa (Novoseven®).

Glanzmanns' thrombasthenia (GT) is an autosomal recessive disorder of platelet function, characterized by absent or defective expression of the integrin heterodimer αIIb, β3, otherwise known as glycoprotein (GP) IIbIIIa, on the platelet surface, and caused by a molecular defect in either subunit (1).

Mucocutaneous bleeding, excessive physiologic blood loss, and bleeding from trauma or surgery are typical, but spontaneous bleeding is uncommon (2). The in vivo bleeding time (BT) is prolonged in GT, shortening to within the normal range after adequate platelet infusion. This is now more conveniently assessed by the in vitro PFA-100® assay closure time, which also normalizes with treatment (3). Platelet alloimmunization may result in relative or absolute platelet refractoriness, complicating the course of a significant portion (4,5) of the pregnancies and deliveries reported in GT (2,4–6), while postpartum hemorrhage (PPH) appears to be a particular risk (2,5)

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CASE REPORT

The patient is a 34-year-old white woman with GT. At age 15 years, she started to experience anaphylactoid reactions to platelet infusions, and was found to have HLA-A11 antibodies.

Early in her first pregnancy, at age 29 years, a type II placenta previa caused six small antepartum hemorrhages, each arrested with random donor platelet infusion. Two packs of HLA-matched platelets were given before induction at 39 weeks. At delivery, a PPH of at least 1,150 mL was arrested by two packs of HLA-matched platelets and additional uterotonic drugs. On day 8 she had another large PPH, which ceased with non-HLA-matched platelets, uterine evacuation, and uterotonic drugs.

At 32 years the patient underwent a lumbar diskectomy for a residual injury following a traffic accident. The operation was preceded by one pack of HLA-matched platelets, and was initially uneventful, until a perioperative dural tear resulted in hemorrhage. Despite local compression and another pack of HLA-matched platelets, significant blood loss continued. Emergency treatment with 4.8-mg intravenous rVIIa (Novoseven®) was given, which immediately arrested the bleeding. Subsequently four packs of non-

HLA-matched platelets were given and further bleeding from the drain was managed by platelet infusions. Approximately 2 weeks after surgery HLA-A1 antibodies appeared in the patient's serum.

The patient had a second child at age 34 years. Four packs of HLA-matched platelets were given before induction of labor and another three after delivery. This approach led to minimal blood loss (100 mL). Two further packs were given on the first postpartum day.

The partner of the patient was shown to be HPA group compatible during the first pregnancy, and does not express HLA-A1 or A11. GPIIbIIIa isoantibodies, and other HPA antibodies were not detected in the patient by monoclonal antibody immunofluorescence platelet assay during either pregnancy.

Recently GPIIbIIIa isoantibodies have been detected on routine screening.

COMMENT

Major bleeding episodes and surgery in GT are managed conventionally with platelet infusion to correct hemostasis, while minor bleeding episodes are treated conservatively. In comparison with acute thrombocytopenia, little has been published on the optimal management of platelet function disorders during invasive procedures such as surgery or childbirth. It is reasonable to believe the same platelet dose per kilogram body weight can be applied. Published guidelines recommend a transfused platelet concentration of 50×10^9 for normal parturition and minor surgery, and 100×10^9 for major surgery and life-threatening bleeding (7), and also that the BT should be brought within the normal range (8).

The quantity of platelets required to achieve the above figures, the effective dose (ED), may be calculated from the patient's blood volume (7). Platelet recovery can be measured by flow cytometry, using a label for GPIIbIIIa to identify platelets bearing $\alpha IIb\beta 3$, at a set interval after infusion. It progressively falls with time due to platelet consumption and senescence. Normally it is approximately 67% 1 hour after infusion, due to splenic sequestration, but may be very much lower if antiplatelet antibodies, bleeding, or sepsis are present.

As platelets are lost or sequestrated in the spleen they need to be replaced for instance during long procedures and in the postoperative period. Excessive blood loss or an increasing PFA-100® indicate the need for further viable platelets.

Consistent management of GT is difficult, with each patient requiring individual assessment and planning. In an emergency, the complicating factors may distract from management of the basic defect. We propose an algorithm to provide a relatively simple framework, which may be adjusted according to individual variations in platelet recovery, etc (Fig. 1). It is significant that when this approach was used in the second delivery, it passed without untoward events, while her previous delivery, which was undoubtedly covered with insufficient platelet dosage, was complicated by hemorrhage. A combination of inadequate platelet dose and a newly formed HLA-antibody are implicated in the excessive blood loss during the spinal surgery.

Prevention of alloimmunization by reflective transfusion practice reduces the incidence of platelet refractoriness, for instance leukodepletion was demonstrated by the TRAP study to reduce alloantibody production in patients receiving platelets over a few months (9). Single donor products appeared to have no additional advantage in this study; however, GT patients are exposed to blood products over a long period making it desirable to give HLA-matched products. Nevertheless one is obliged to use random donor platelets in an emergency until HLA-matched packs are available. A normal PFA-100® closure time should be obtained before commencing elective procedures particularly if alloantibodies are present. In an emergency, a very large platelet dose may be effective albeit at the risk of further antibody stimulation. Excessive blood loss, particularly with a normal PFA-100® closure time, should provoke a search for other causes.

It is prudent to test for anti-HLA antibodies and GPIIbIIIa isoantibodies before elective surgery, following episodes of inadequate response to platelets, and also in pregnancy because thrombocytopenia has been noted in the babies of alloimmunized thrombasthenic mothers (6).

If HLA-antibodies are present, HLA-matched platelets may improve recovery, but HLA-compatible platelets give a more variable response. HLA-stripped platelets, which can be prepared at short notice, may prove valuable once further studies have been completed (10).

GPIIbIIIa isoantibodies react with all donor platelets however platelet crossmatching has been shown to select platelet units with good recovery in vivo (11). Platelet crossmatching also

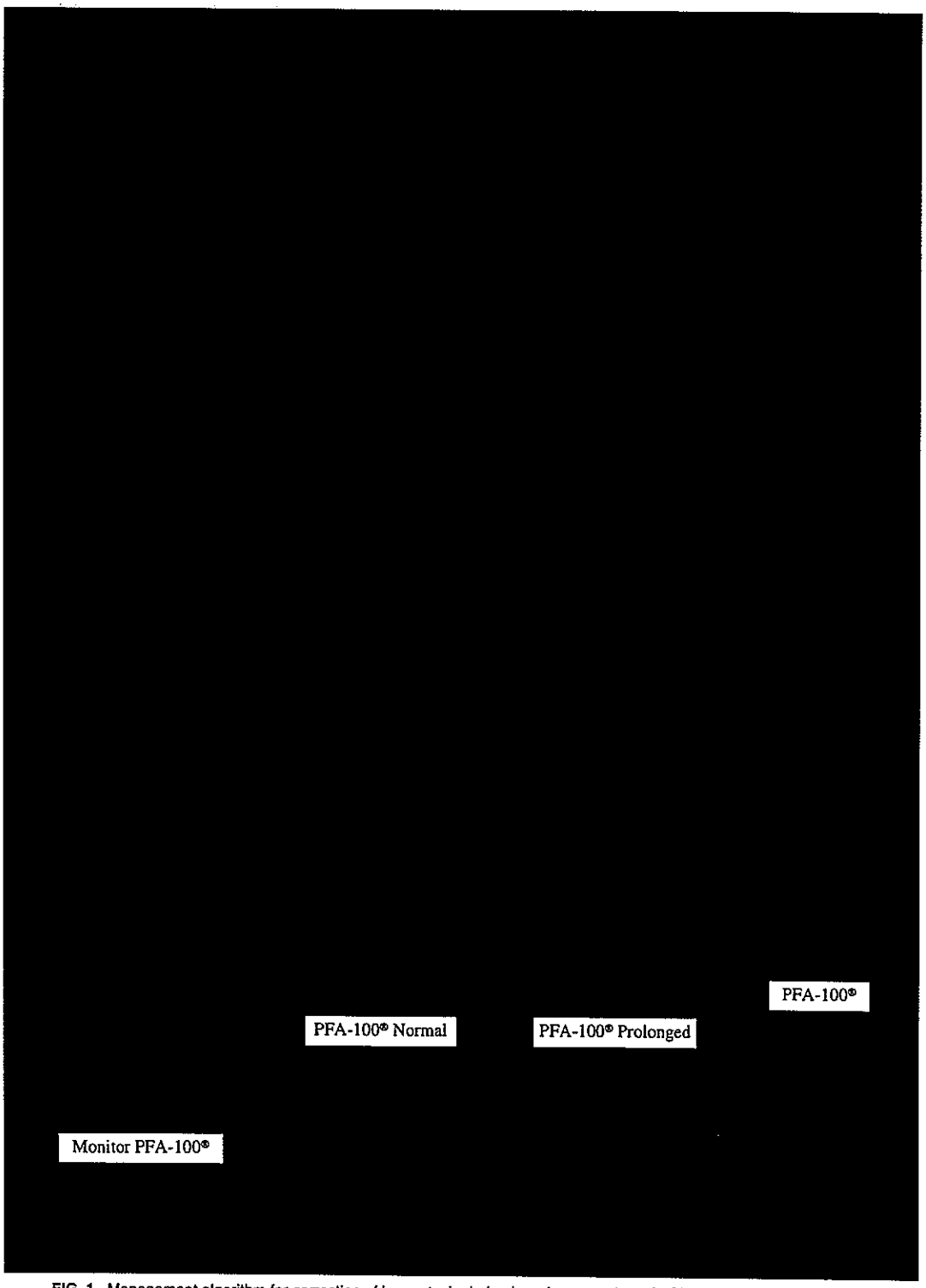

FIG. 1. Management algorithm for correction of hemostasis during invasive procedures in Glanzmann's thrombasthenia. Abs = antibodies, NR = platelet nonrefractory, R = platelet refractory.

identifies platelet packs likely to provide a larger increment in the presence of HLA-antibodies (12).

In the past, absolute refractoriness has been successfully managed in emergency by antibody removal by plasmapheresis (5), or by intravenous immunoglobulin (4) followed by platelet infusion. Today rVIIa is used in addition to platelets if platelet response is poor, particularly if GPIIbIIIa isoantibodies are present, or if high-risk sites are involved, such as brain, spinal cord, or where compartment syndrome may form. This appears to correct hemostasis via thrombin generation (13), but needs non-thrombasthenic platelets to form a normal clot. Antifibrinolytic drugs increase the hemostatic effect (14), which may be monitored by PFA-100®. Repeat doses (2-hourly) are necessary because it has a short half-life, and precise regimens are yet to be established in pregnancy (15). Its long shelf life makes it ideal for those in geographically isolated areas (14) and also pregnant women where obstetric emergency may necessitate immediate delivery. Epidural anesthesia is considered an unnecessary risk because platelet function cannot be guaranteed.

A particular risk in GT is PPH, reduced by modern obstetric practices and prolonged uterine contraction. Caesarian section may reduce the risk of PPH possibly by more thorough uterine evacuation (2), but late PPH remains a risk until the placental site heals.

In the future, rVIIa may become the treatment of choice with its good side effect profile (16), absence of platelet sensitization, and rapid effect, and may be useful as a prophylactic agent postpartum.

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