Heparin-induced thrombocytopenia in pregnancy: an interdisciplinary challenge—a case report and literature review

E. Mauermann,[a] C. Vökt,[b] D.A. Tsakiris,[c] D. Tobler,[d] T. Girard[a]
[a]*Department for Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland*
[b]*Department of Obstetrics, University Hospital Basel, Basel, Switzerland*
[c]*Diagnostic Hematology, University Hospital Basel, Basel, Switzerland*
[d]*Department of Cardiology, University Hospital Basel, Basel, Switzerland*

ABSTRACT
Heparin-induced thrombocytopenia is a serious adverse event of anticoagulation with a high risk of thromboembolic complications. As a consequence, anticoagulants other than heparins must be administered. These may be unavailable, contraindicated during pregnancy, off-label, impractical due to short half-lives and, most importantly, may be unfamiliar to many anesthesiologists. Impaired coagulation bears the risk of adverse events following neuraxial procedures and of peripartum hemorrhage. We describe the case of heparin-induced thrombocytopenia in a 29-year-old pregnant woman at 27 weeks of gestation with severe valvular heart disease.

Keywords: Heparin-induced thrombocytopenia; Fondaparinux; Anticoagulation

Introduction

Heparin-induced thrombocytopenia (HIT) type II is a rare but serious complication of heparin treatment in which over 50% of untreated patients develop thrombosis.[1] It arises as a result of IgG-PF4 antibody complexes binding and activating platelet Fcγ RIIa receptors, thereby causing intense platelet activation and the release of procoagulatory microparticles.[2] While HIT is rare in pregnancy (<0.1%),[3] the impact of anticoagulation modalities on management options for labor and delivery is immense due to the pre-existing physiological hypercoagulability, the potential adverse events associated with neuraxial procedures, and the risk of peripartum hemorrhage.

Case report

A 29-year-old G3P2 woman weighing 50 kg presented to the emergency room at 27 weeks of gestation with New York Heart Association class IV signs of congestive heart failure (i.e. symptoms of heart failure at rest). It was almost impossible to obtain a medical history because the patient had recently entered the country and did not speak any European languages. Initial investigations showed dilated cardiac chambers with a left atrial volume of 435 mL, severe mitral regurgitation (effective regurgitant orifice area 0.8 cm^2), moderate mitral stenosis (mean gradient 9 mmHg), mild aortic stenosis and mild tricuspid regurgitation. She was anemic with a hemoglobin count of 7.8 g/dL. The patient had experienced preterm premature rupture of membranes 20 days before presentation. Obstetric examination revealed intrauterine growth restriction, oligohydramnios and placental insufficiency.

She was transferred to the intensive care unit and initially stabilized with intravenous digoxin, furosemide, potassium and magnesium. She also received amoxicillin as antibiotic prophylaxis and betamethasone for fetal lung maturation. Maintenance of perfusion pressures required a norepinephrine infusion. She was anticoagulated with 15000 U/24 h of unfractionated heparin on the day of admission and with 10000 U/day subcutaneous dalteparin thereafter. On the second day she was clinically better with no dyspnea, reduced heart rate, acceptable blood pressure and no longer required norepinephrine. She was transferred to a peripheral ward, where she received further monitoring and treatment including beta blockade and injectable iron.

On Day 8 of hospitalization the platelet count decreased from an initial value of 254×10^9/L to 121×10^9/L. Her 4T score (the most commonly used HIT score[4]) was six out of a maximum eight points,

Accepted November 2015
Correspondence to: Prof. Thierry Girard, Department for Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland.
E-mail address: Thierry.Girard@usb.ch

indicating a positive predictive value for HIT of 67%.[5] Dalteparin was stopped and hematological advice sought. The diagnosis of HIT was confirmed two days later by IgG ELISA. Daily oral aspirin 100 mg and subcutaneous fondaparinux 2.5 mg were started with a target specific anti-Xa activity of >0.25 mg/L.

The plan for delivery included an interval of 36 h between the last dose of fondaparinux and any neuraxial procedure. Hematological opinion recommended the use of tranexamic acid, platelets and rFVIIa if acute peripartum hemorrhage occurred before the residual effects of fondaparinux and aspirin had worn off. At 32 weeks of gestation, the patient's computerized cardiotocogram suggested severe placental insufficiency. After interdisciplinary consultation, caesarean delivery was scheduled for the following morning, 36 h after the last dose of fondaparinux. We did not specifically determine fondaparinux activity immediately before surgery as the patient had a normal glomerular filtration rate and fondaparinux levels had consistently been within the target range in the days before surgery.

A translator was present in the operating room. Light sedation with intravenous remifentanil (maximum 0.7 μg/kg/min) was used to minimize patient distress. Arterial and central venous cannulae were placed and a combined spinal-epidural anesthetic was performed using intrathecal hyperbaric bupivacaine 7 mg, fentanyl 10 μg and morphine 100 μg. Small amounts of vasoactive drugs (esmolol, metoprolol, and norepinephrine) were required. Oxytocin 3 U were administered by slow infusion. No intraoperative complications occurred. Estimated blood loss was 400 mL; crystalloid 1000 mL was administered and postoperative hemoglobin was 9.9 g/dL. Postoperative care was uneventful. Fondaparinux 5 mg daily was re-administered 12 h after surgery followed by oral anticoagulation with vitamin K antagonists (target INR 2.5). The baby weighed 950 g and was transferred to the neonatal intensive unit due to prematurity. Apgar scores were 6, 7 and 7 at 1, 5 and 10 min, respectively. Six months after delivery the patient underwent mitral valve replacement and tricuspid valve reconstruction.

Discussion

Heparin-induced thrombocytopenia is a potentially fatal adverse drug reaction resulting from heparin treatment, and presents with a decrease in platelets but a paradoxical increase in thrombotic risk due to antibody mediated platelet activation. The pathogenesis of HIT is an immune response to heparin. Platelet factor 4 (PF4) is released from platelet α-granules and binds heparin and other polyanions, building a complex against which B lymphocytes form IgG antibodies.[6] The Fc segment of the IgG antibodies binds to platelet Fcγ RIIa receptors activating, aggregating and consuming platelets in addition to releasing microparticles and triggering the coagulation cascade.[2] These antibodies also activate monocytes and endothelial cells, leading to an increase in tissue factor expression and thrombin generation.[6]

It has recently been re-emphasized that HIT should be viewed as a clinical-pathological syndrome,[7] meaning that both the clinical context and the existence of platelet-activating, heparin-dependent antibodies are indicative of HIT.[8] Only a small proportion of those patients exhibiting PF4 antibodies may develop clinical HIT.[9,10]

Clinical suspicion of HIT may be confirmed by the traditional and easy to calculate 4T score,[4,11] or the newer HIT Expert Probability (HEP) score.[12] A recent study showed no significant difference between the scores.[13] The 4T score examines the extent of Thrombocytopenia, Timing of thrombocytopenia, Thrombosis or other sequelae, and likelihood of oTher causes of thrombocytopenia. After assigning each of the categories 0, 1 or 2 points, patients may be divided into low (0–3 points), moderate (4–5 points) and high (6–8 points) risk.[4,14] A recent meta-analysis showed positive predictive values of 0.64 (95% CI 0.40 to 0.82) and 0.14 (95% CI 0.09 to 0.22) for high and moderate risk 4T scores, while the negative predictive value of a low 4T score was 0.998 (95% CI 0.97 to 1.00).[5]

Laboratory tests include traditional antigen assays such as IgG ELISA or heparin/platelet factor 4 particle gel immunoassay, and functional assays such as heparin-induced platelet activation (HIPA) or serotonin release assay (SRA). The main problem with the readily available traditional antigen assays is that heparin-treated patients often generate PF4 antibodies incapable of causing HIT, so a positive test does not equate to clinical HIT.[11] The optical density of antigen tests which correlates with antibody activity is generally used; a cut-off of 0.4 indicates a positive test.[15,16] It has been estimated that only 15% of positive antigen assay tests are really positive, as determined by SRA.[17] To improve sensitivity, it has been suggested that the cut-off is increased to an optical density (a measure of assay reactivity) of 1.0,[17] although this remains controversial.[18] Functional assays are based on the activation of platelets by IgG-HIT antibodies,[19] but are only available in specialized laboratories and may take days to perform. Further assays are in development, but current algorithms suggest using a risk score combined with a traditional antigen assay, and perhaps a functional assay.[6,10] In our institution, a cut-off of 0.5 is used.

Several factors complicate HIT and its management in pregnancy, particularly the hypercoagulable state.[20] In pregnancy, heparin is generally a safe first-line treatment[21] and HIT is rare.[3,22] A clinical suspicion of HIT (e.g. a 4T score >3) mandates immediate heparin cessation and switching to a non-heparin anticoagulant,