

Letter to the Editor

Perioperative Coagulation Management in a Patient with Congenital Afibrinogenemia during Revision Total Hip Arthroplasty

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We read with great interest the article by Casini et al¹ describing clinical features and management of congenital fibrinogen deficiencies, which was published along with other interesting articles related to such disorders in a recent issue of *Seminars in Thrombosis & Hemostasis*.² We therefore wish to report the only case of congenital afibrinogenemia in Slovakia with a successful perioperative management of hemostasis during revision total hip arthroplasty.

Congenital afibrinogenemia is an autosomal recessive bleeding disorder that refers to the total absence of fibrinogen, as measured by an antigenic assay.¹ This disorder is caused by variations in the *FGA*, *FGB*, and *FGG* genes, which encode the fibrinogen $\alpha\alpha$, $\beta\beta$, and γ chains, respectively. Afibrinogenemia is associated with homozygous or compound heterozygous mutations, and hypofibrinogenemia is usually linked with heterozygous mutations.^{3,4} The estimated prevalence of afibrinogenemia is around 1 in 1,000,000,⁴ although in Slovakia we estimate it to be 1 in 5,000,000.⁵

The commonest manifestation of the disease is bleeding from mucosal surfaces; however, musculoskeletal bleeding, gynecologic and obstetric complications, spontaneous bleeding, bleeding after minor trauma and during interventional procedures, or thromboembolic episodes have also been reported.⁶ Absence of immunoreactive fibrinogen is essential for the diagnosis of congenital afibrinogenemia. All coagulation tests that depend on the formation of fibrin as the end point, that is, prothrombin time (PT), activated partial thromboplastin time (aPTT), or thrombin time (TT), are infinitely prolonged.^{1,4} Fibrinogen replacement therapy, particularly the most widely used plasma-derived fibrinogen concentrate, is considered as the treatment of choice in spontaneous

bleeding episodes and as prophylaxis before surgical procedures or against spontaneous bleeding in patients with congenital and acquired fibrinogen deficiency.^{1,7}

We herein report the successful perioperative management of hemostasis during revision total hip arthroplasty in a 26-year-old man we have previously reported with congenital afibrinogenemia and a homozygous point mutation in exon 4 (Gln180Stop) of *FGB* gene.⁸ Early after birth, the patient experienced umbilical cord bleeding and development of epidural hematoma and hygroma in the occipital region with the need of neurosurgical evacuation. In the patient's history, there were many further bleeding episodes, including repeated hemorrhage into joints, muscles, mucocutaneous bleeding, and bleeding into soft tissues. This patient was managed with prophylactic intravenous administration of fibrinogen concentrate at the dose of 2 g once a month from the age of 15 years.⁵ Since then, he had significant reduction in the intensity and frequency of spontaneous bleeding.

The patient developed coxitis, or inflammation of the hip, in August 2002 due to microbleeds into the joint capsule. Coxitis was one of the most devastating complications of the patient's disease, and the implantation of a total hip endoprosthesis appeared the only possible treatment option. This was performed in the patient at age 15 years. One day before surgery, laboratory screening indicated grossly prolonged results for PT, aPTT, and TT (all of them > 300 s). Platelet count ($230 \times 10^9/L$) and hemoglobin (151 g/L) were in the normal range; however, fibrinogen according to the Clauss procedure was undetectable.

Owing to the rarity of afibrinogenemia, little is known about the optimal perioperative management of patients with this disease, including the pharmacokinetics of fibrinogen

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Fig. 1 Postoperative X-ray after the revision total hip.

concentrate.⁹ In a survey conducted by Bornikova et al, the authors noted that for patients in surgical cases with satisfactory hemostasis, a plasma fibrinogen level ranging from 100 to 200 mg/dL was achieved at the time of surgery.⁷ Preoperatively, the patient received fibrinogen concentrate (Haemocomplettan P, CSL Behring, Marburg, Germany) in the dose of 75 mg/kg (6 g of fibrinogen concentrate, weight of the patient 80 kg). This dose increased the patient's level of fibrinogen after 2 hours to a rate corresponding to 170 mg/dL. Intravenous administration of fibrinogen concentrate also led to a rapid change of previously unmeasurable PT, TT, and aPTT values to detectable values. These

data were similar to those reported by Négrier et al.¹⁰ Thus, as demonstrated here and previously, patients can successfully be treated with a wide range of target fibrinogen levels and duration of treatment. This decision may be influenced by the severity of the deficiency and the invasiveness of the surgical procedure. The surgery itself lasted 3 hours under general anesthesia. During surgery, the patient received fibrinogen concentrate in the dose of 25 mg/kg. The estimated blood loss was 800 mL. The patient was given an intraoperative transfusion 499 mL (2U) of packed red blood cells and 380 mL of auto transfusion. Immediately after surgery, the level of fibrinogen achieved was 110 mg/dL. X-ray showed acceptable positioning and alignment of the implants (►Fig. 1). Postoperatively, the patient's fibrinogen levels were checked twice a day.

Twenty-four hours after surgery, fibrinogen concentrate was given to the patient at the dose of 37.5 mg/kg every 8 hours. The level of plasma fibrinogen was maintained above 130 mg/dL. One day after surgery, fibrinogen concentrate was administered at the dose of 37.5 mg/kg every 12 hours with a targeted level of fibrinogen in the range of 130 to 150 mg/dL. Two days after surgery, the fibrinogen concentrate administration was reduced to a dose of 25 mg/kg every 12 hours. This dose was given during the next 5 days. In this period, the fibrinogen activity was retained in the range of 170 to 210 mg/dL. On the sixth and seventh day after surgery, the reduced dose of fibrinogen concentrate was continued at 12.5 mg/kg every 24 hours. During these days, the level of fibrinogen ranged as high as 120 to 140 mg/dL. Between 8th and 12th day after surgery, we administered the fibrinogen concentrate at the dose of 12.5 mg/kg once every 48 hours. As the surgery required thorough hematological management, there was a need to ensure fine adjustment of the balance between the administration of fibrinogen concentrate and thromboprophylaxis. Accordingly, after surgery, the administration of fibrinogen concentrate was combined with low-molecular-weight heparin (nadroparin) at the dose of 0.3 mL (2,850 IU) daily. Immediately after surgery, there were no signs or symptoms of excessive bleeding. The patient was discharged safely at the 12th day after surgery with a level of plasma fibrinogen above 50 mg/dL (►Fig. 2).

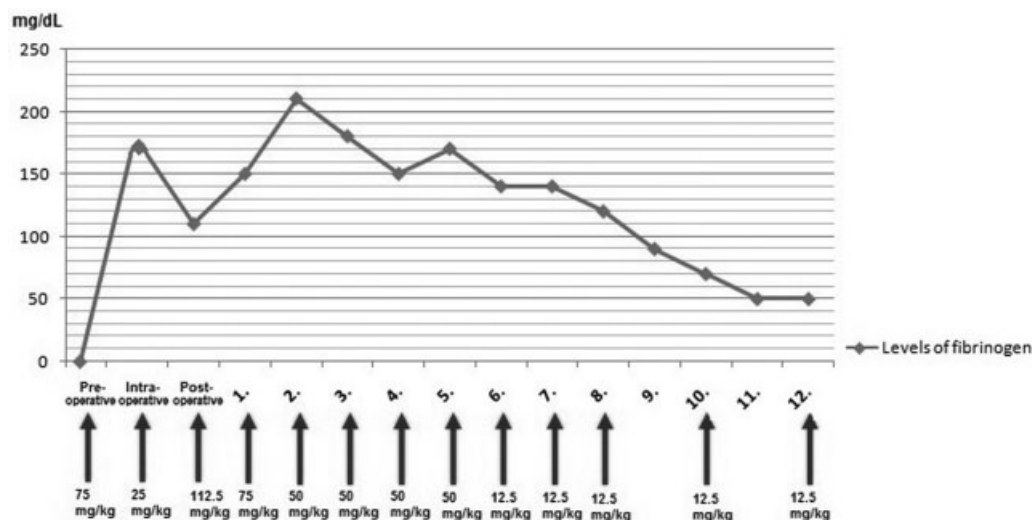


Fig. 2 The levels of fibrinogen measured preoperatively, intraoperatively, and postoperatively together with fibrinogen replacement therapy.



Fig. 3 Decentration of the femoral head and incipient osteolytic lesions below the acetabulum.

Regular orthopedic checks once a year were recommended. Unfortunately, 10 years later, from March 2014, the patient started to limp with a frequent and gradually disabling pain localized in the left hip. Control X-ray examination showed protrusion of the femoral head with the thinning of the inlay 4 to 5 mm and incipient osteolytic lesions below the acetabulum with the necessity of surgical revision (→Fig. 3).

The management of thrombotic complications in patients with afibrinogenemia is problematic because of their bleeding tendency. Some authors recommend use of compression stockings and low-molecular-weight heparin in patients with a history of thrombosis who are undergoing surgery.¹¹ In patients who develop thrombotic complications following replacement therapy, some authors continue the latter if indicated and co-administer low-molecular-weight or unfractionated heparin. Our patient and members of the family have not experienced any thrombotic episodes. Furthermore, screening tests for thrombophilic mutations in the family have been negative. Therefore, thromboprophylaxis was applied at the dose of 0.3 mL daily only during hospitalization.

Our patient has otherwise been managed with prophylactic administration of fibrinogen concentrate at the dose of 25 mg/kg once a month from the age of 15 years before

surgery.⁵ We managed the patient during intensive rehabilitation with prophylactic dose fibrinogen concentrate once a week within 2 months after surgery. At present, the patient is given a prophylactic dose of 25 mg/kg of fibrinogen concentrate once every 2 weeks and he is without any bleeding or thrombotic complications.

In conclusion, our results in this patient with congenital afibrinogenemia who underwent the successful repeated total left hip arthroplasty reaffirm the recommendation to tailor treatment to ensure a hemostasis balance between the replacement of clotting factor (fibrinogen concentrate) and thromboprophylaxis.

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