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Arthroplasty in patients with rare conditions

Total knee arthroplasty in a patient with hypofibrinogenemia

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ABSTRACT

Patients with afibrinogenemia or hypofibrinogenemia present a unique challenge to the arthroplasty surgeon as fibrinogen is a key contributor to hemostasis. Patients with these disorders are known to have a higher risk for postsurgical bleeding complications. We present the case of a patient with hypofibrinogenemia who underwent an elective total knee arthroplasty. Our colleagues in hematology-oncology guided us initially to achieve and maintain appropriate fibrinogen levels in the early perioperative period. However, the patient developed an acute joint effusion and subsequent infection 4 weeks after her initial operation. Her fibrinogen levels were noted to have fallen below the target range by that time, and it was also revealed that the patient failed to follow-up with hematology-oncology to monitor her levels. Based on our review of the available literature, we recommend that patient's fibrinogen levels be closely monitored and maintained ideally >100 mg/dL not only in the initial perioperative window but perhaps for the first 4-6 weeks postoperatively as well.

Introduction

Afibrinogenemia and hypofibrinogenemia, defined as plasma fibrinogen levels <150 mg/dL, are rare coagulation disorders with an incidence of 1 in 1 million [1,2]. Of all coagulation disorders, fibrinogen deficiency has been reported approximately 8% of the time [3].

Fibrinogen serves as a key contributor to hemostasis by assisting in clot formation, platelet aggregation, and fibrinolysis [4,5]. Treatment for congenital fibrinogen deficiency can consist of replacement with fresh frozen plasma (FFP), cryoprecipitate (cryo), or fibrinogen concentrate (FC). Clinically, symptoms may vary depending on the severity of the deficiency. Patients with hypofibrinogenemia are typically asymptomatic; however, they may be at risk for bleeding complications when exposed to trauma, pregnancy, or surgery. Those with afibrinogenemia tend to have a higher frequency of bleeding in comparison [3,4].

Unfortunately, there is limited literature and a lack of guidelines regarding the optimal perioperative management of these patients. The few reported cases consist of those with severe or complete deficiency of fibrinogen in the setting of trauma and pregnancy where significant bleeding is often expected [6]. In all cases, current recommendations suggest maintaining fibrinogen level above 100-200 mg/dL to prevent bleeding complications [2,7,8]. Currently, no clinical cases, guidelines, or recommendations exist for patients with congenital fibrinogen deficiency undergoing total joint arthroplasty.

We report the case of a patient with congenital hypofibrinogenemia who underwent an elective total knee arthroplasty (TKA) and unfortunately suffered a postoperative hemarthrosis and acute prosthetic joint infection. We discuss our experience with the perioperative management of this challenging patient.

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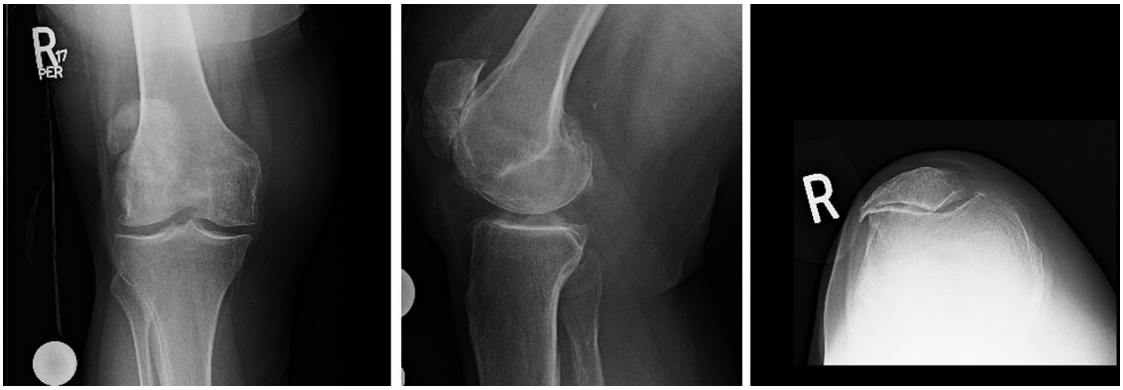

Figure 1. Preoperative radiograph of the patient showing osteoarthritic changes which unfortunately not managed sufficiently with nonoperative measures.

Case history

A 67-year-old female had a medical history significant for hypofibrinogenemia and right knee pain related to moderate tricompartmental osteoarthritis. Of note, written informed consent was obtained from the patient for publication of this case report and accompanying images. She presented to our institution after a fall resulting in a closed right patella fracture with an intact extensor mechanism, which was treated conservatively. She continued to complain of right knee pain despite radiographic evidence of complete fracture healing. Physical examination and subsequent radiographs suggested that her ongoing discomfort was more likely secondary to worsening tricompartmental arthritis, particularly involving the patellofemoral joint (Fig. 1). Given her active functional status, it was determined that she would benefit from a total knee arthroplasty.

Her family history was significant for a grandmother who died because of hemorrhagic shock while delivering her father, as well as a daughter with known hypofibrinogenemia. The patient's surgical history is significant for a wisdom tooth extraction, vaginal delivery, gastric band placement, and colectomy for diverticulitis without any significant bleeding episodes. She was diagnosed with hypofibrinogenemia based on abnormal coagulation profile laboratory values obtained due to the positive family history that had prompted an in-depth hematology workup.

Before her elective right TKA, her preadmission laboratories demonstrated a fibrinogen level of 58 mg/dL (normal range: 150-480 mg/dL), international normalized ratio (INR) of 1.3 (normal range: 0.8-1.2), prothrombin time (PT) of 13.2 seconds (normal range: 9.5-12.5 seconds), and activated partial thromboplastin time (aPTT) of 31 seconds (normal range: 24-37 seconds). Hematology was consulted for perioperative management and recommended

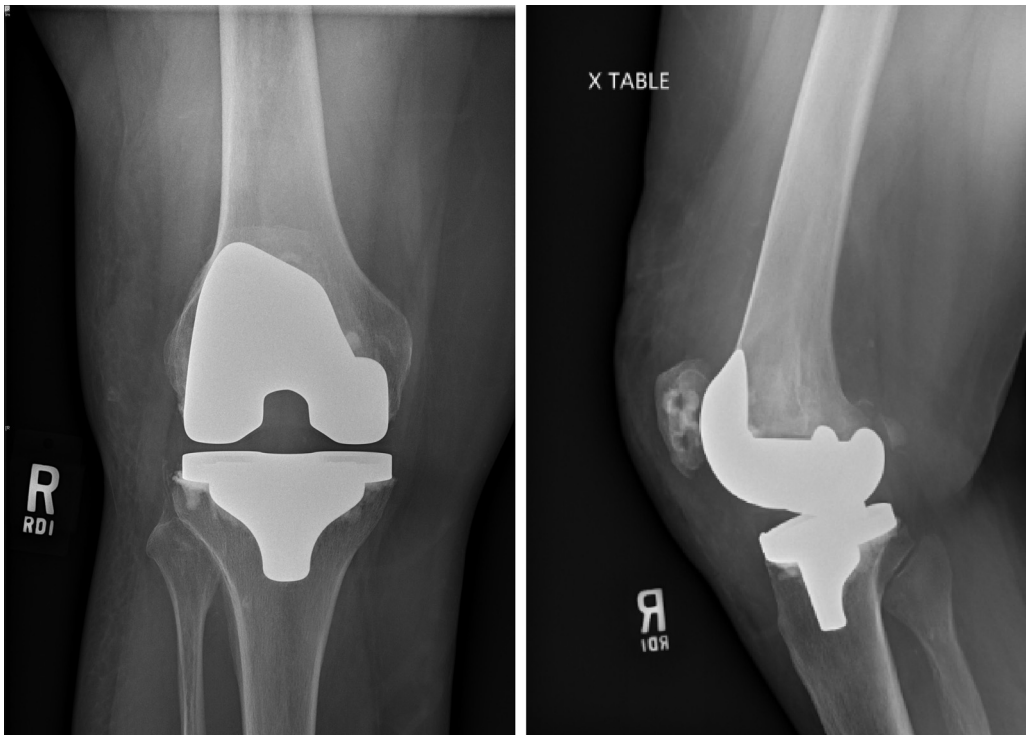

Figure 2. Postoperative radiographs after the index operation for the total knee replacement.

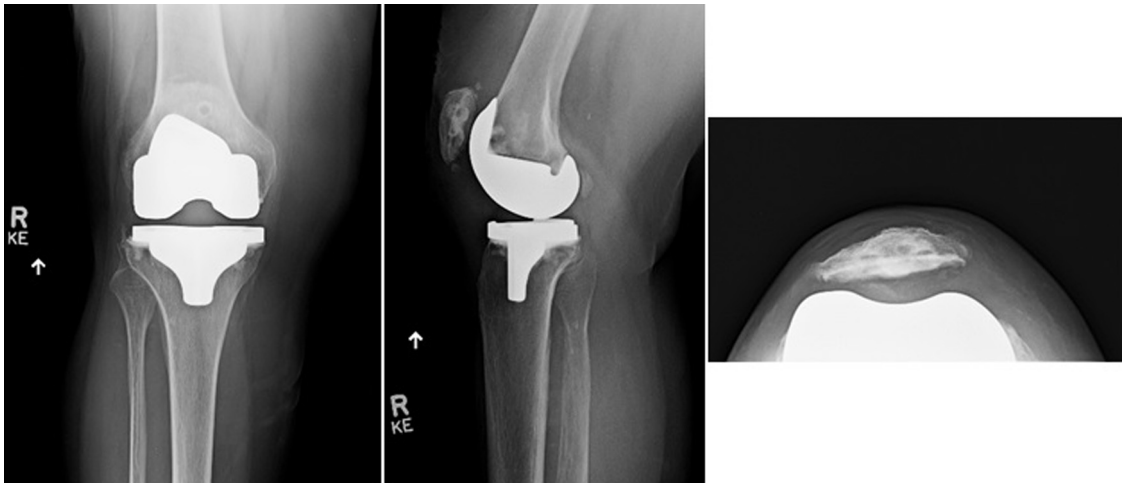

Figure 3. Radiographs of the patient showing stable alignment at her most recent clinic visit after the operation for the joint infection.

that she receive 15 units of cryo 4 hours before the procedure in the hospital's infusion center. Accordingly, the patient received 875 mg of fibrinogen (~10 mg/kg) raising her preoperative fibrinogen level to 116 mg/dL, immediately before the TKA, which was then performed on the same morning after the infusion.

At the time of surgery, a standard medial parapatellar approach was used. The synovium and articular cartilage were noted to be grossly stained with brown hemosiderin deposition. The case was uneventful without any intraoperative complications or excessive bleeding. Hemostasis was actively achieved throughout the operation; the tourniquet was inflated only for final bony preparation and cementation for 30 minutes, and the estimated blood loss was 100 mL.

The surgical incision was closed in a standard multilayered fashion with absorbable sutures, followed by the injection of 1000 mg of intra-articular tranexamic acid for topical hemostasis, which is the current standard of care at our institution [9]. She received our institution's routine perioperative prophylactic antibiotic regimen of 2-g cefazolin and also had 1.2 g of tobramycin mixed with the bone cement for the implant. A compressive dressing was applied along with a knee immobilizer after the procedure. These were used to rest the knee joint and minimize tissue shear,

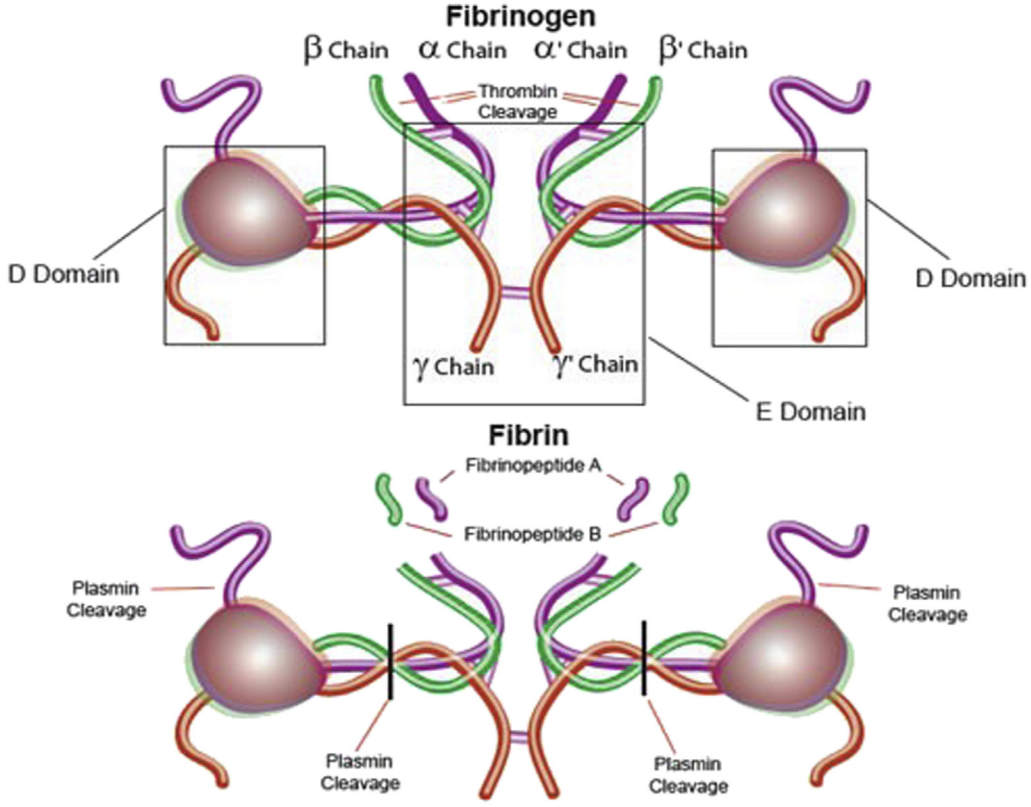

Figure 4. The structure of fibrinogen showing the two identical polypeptide chains that constitute the protein. (Adapted: The Plasma Proteins, 2nd ed., 2, Putnam, F.W., ed, p. 148).

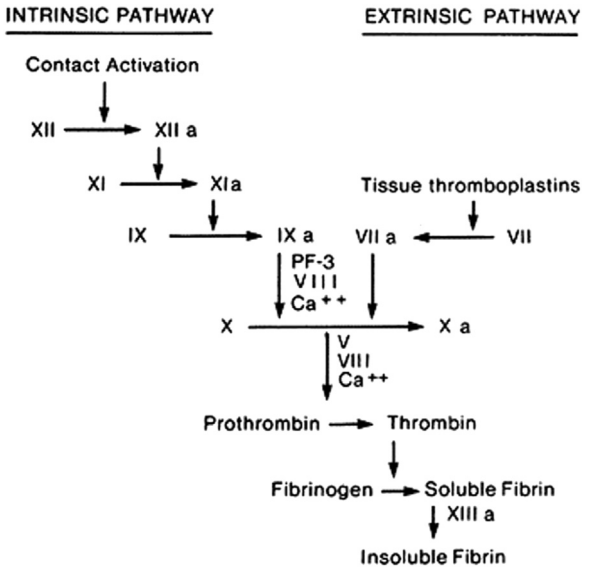

Figure 5. Simple coagulation cascade showing the role of fibrinogen (http://imgbuddy.com/simple-coagulation-cascade.asp).

intended to be kept in place for a total of 7 days postoperatively to reduce the risk of postoperative hemarthrosis. She was allowed to bear weight as tolerated during that time with the knee straight. Postoperative radiographs showed acceptable positioning and alignment of the implants (Fig. 2).

Postoperatively, the patient's fibrinogen levels were checked daily and maintained above 100 mg/dL throughout her 3-day inpatient stay. As per our protocol, she received oral 325-mg enteric-coated aspirin twice daily for deep vein thrombosis prophylaxis for 30 days. Her immediate postoperative course was otherwise unremarkable without any signs or symptoms of excessive bleeding. She was discharged safely to home on postoperative day 3.

Twenty-five days after her index procedure, the patient presented to the emergency department with an acute onset of right knee swelling and worsening pain. The patient noted a recent increase in her level of activity because of a strenuous physical therapy regimen but denied any subjective fevers or chills. Her white blood cell count at the time of presentation in the emergency department was 12.1 $\times 10^3/\mu L$, erythrocyte sedimentation rate and C-reactive protein level were 8 mm/h and 7.36 mg/L, respectively, and fibrinogen level was 60 mg/dL. The patient's knee was aspirated given the concern for infection. Synovial analysis revealed a milky, white fluid with a nucleated cell count of 3778/CMM and a neutrophil count of 100%. Gram stain showed moderate gram-positive cocci and the final culture grew methicillin-sensitive *staphylococcus aureus*.

A decision was made to return to the operating room for irrigation and debridement, along with polyethylene exchange and implant retention. Gross purulence along with old hematoma in the knee joint was noted at the time of the surgery. Intraoperative cultures were also consistent with methicillin-sensitive *staphylococcus aureus*. The patient was discharged on a 6-week course of cefazolin and rifampin as recommended by the Infectious Disease service. Close follow-up was arranged with orthopaedic surgery, infectious disease, and hematology. Her fibrinogen levels after the second operation were checked weekly with a goal of maintaining a level >100 mg/dL for a minimum of 4 weeks.

On most recent 1-year follow-up from her index procedure, she reported good overall knee function with minimal discomfort. She had returned to performing most of her activities of daily activities with minimal limitations. Her documented range of motion was 0-124°. There were no clinical signs of residual infection, and her C-reactive protein value was 6.2. Imaging at this time demonstrated satisfactory component alignment (Fig. 3).

Discussion

This is the first reported case of a patient diagnosed with hypofibrinogenemia undergoing an elective TKA. Patients with hypofibrinogenemia are typically asymptomatic at baseline but remain at risk for hemodynamic complications after trauma or surgery [10,11]. Previous case reports have demonstrated that patients with afibrinogenemia may experience significant postoperative bleeding [11]. Postoperative bleeding is a known contributor to the development of deep infection, which has been consistently demonstrated in the hemophiliac patient population [12,13]. Because of this potential risk, current hematology practice includes prophylactically treating the patient in advance of elective procedures to raise serum fibrinogen levels >100 mg/dL in the immediate perioperative period. It remains unclear how long this level should be maintained, or how frequently fibrinogen levels should be checked, particularly when considering elective arthroplasty.

Epidemiology

Congenital fibrinogen disorders are among the rarest bleeding disorders [1,3-5,7,10,14,15]. Researchers estimate an incidence of 1 in 1 million within the general population [4]. The prevalence of this disorder appears to be similar in men and women. Patients with homozygous mutations exhibited complete fibrinogen deficiency, whereas those with a heterozygous mutation experienced abnormal bleeding during pregnancy and after trauma [3].

Genetics

Fibrinogen is a glycoprotein that is composed of two identical polypeptide chains (Fig. 4). Each one of these chains is a compilation of three genetically unique polypeptides (alpha, beta, and gamma), which are all located on chromosome 4 and are susceptible to mutations, resulting in clinical deficiency [15,16].

Congenital disorders of fibrinogen may result from production of an abnormal protein (dysfibrinogenemia), a reduction (hypofibrinogenemia) or a complete lack of production (afibrinogenemia) [5]. Over 90% of mutations responsible for dysfibrinogenemia are missense mutations at a functionally or structurally active site of the polypeptide [14]. Patients with hypofibrinogenemia or afibrinogenemia usually suffer from a truncating mutation in the alpha chain that prevents a functionally significant portion of the protein from being synthesized [15]. The patient reported in this study was diagnosed with hypofibrinogenemia.

Pathophysiology

Fibrinogen is a key contributor to hemostasis, assisting with clot formation, platelet aggregation, and fibrinolysis [4,5]. It is the most abundant clotting factor in the human circulation, with normal concentrations typically ranging from 2.0 to 4.5 g/L [10].

As the clotting cascade progresses in the normal individual, fibrinogen is cleaved by thrombin into the active monomer fibrin (Fig. 5). After cleavage, neighboring fibrin monomers polymerize via noncovalent and covalent bonds at the D-domain to form a fibrin clot [17,18]. It is cleavage of this fibrin-fibrin bond at the

D-domain that produces D-dimer, a molecule often measured to evaluate the presence of a clot in the circulatory system.

Diagnosis and laboratory analysis

As with other inherited coagulation disorders, patients may report a history of excessive bleeding when challenged such as during dental extraction or pregnancy. Impaired healing may also be a manifestation. Patients with complete deficiency, afibrinogenemia, may even experience thrombotic events. Of note, in mild cases of hypofibrinogenemia, symptoms often go unnoticed. Such reports or a known family history should prompt a hematology workup initially with a basic coagulation profile including PT, INR, and aPTT. Further analysis of these values may guide further testing. For example, a normal aPTT and prolonged PT/INR may be more suggestive of FVII deficiency, whereas both tests prolonged are nonspecific for many other deficiencies.

In congenital fibrinogen deficiency, PT/INR and aPTT are all elevated to a variable amount depending on the severity of fibrinogen deficiency. The intrinsic and extrinsic pathways both involve fibrinogen in their clotting cascade, and hence, both PT and aPTT are affected. In our patient, both INR and PT were slightly elevated with a normal aPTT. When suspecting a fibrinogen deficiency, fibrinogen can specifically be measured by functional (Clauss method) and/or antigenic assays (enzyme-linked immunosorbent assay). This is typically sought out after a negative workup for less rare disorders such as hemophilia A and B (factor VIII and IX deficiency) [2,3].

Treatment and recommendations

Current options for fibrinogen repletion in deficient patients include FFP, cryo, and FC [1-3,6,7,10,19]. The United Kingdom Haemophilia Centre Doctors' Organisation recommends that fibrinogen levels are maintained >100 mg/dL for hemostasis and >50 mg/dL until wound healing is complete in patients with afibrinogenemia [7]. In a survey conducted by Peyvandi et al. [11], the authors noted that patients experiencing minor bleeding episodes were treated with targeted fibrinogen levels of >100 mg/dL and those with more severe episodes such as central nervous system bleeding were treated with targeted levels of >150 mg/dL. The authors of another study discovered that most cases of inadequate hemostatic control or early bleeding were associated with fibrinogen levels <75 mg/dL. They also noted that in surgical cases with satisfactory hemostasis, a plasma fibrinogen level ranging from 100 mg/dL to 200 mg/dL was achieved at the time of surgery [2].

In addition to a target fibrinogen level, the recommended duration of perioperative treatment also lacks formal guidelines. In a case report by Reidy et al. [8], a patient with afibrinogenemia was successfully treated with a total elbow arthroplasty in which fibrinogen levels were maintained >50 mg/dL in the perioperative and early postoperative periods. The patient was closely monitored with weekly fibrinogen levels and administration of FC for another 18 weeks postoperatively until back on his preoperative regimen. In another case report, a patient with congenital hypofibrinogenemia and a preoperative fibrinogen level of 110 mg/dL undergoing aortic valve replacement/coronary artery bypass grafting was treated successfully for a total of 6 days while inpatient maintaining fibrinogen levels no lower than 280 mg/dL [20]. As demonstrated, 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.

Given the lack of formal guidelines for appropriate management of hypofibrinogenemia after total joint arthroplasty, we chose to maintain fibrinogen levels more than 100 mg/dL for our patient in the immediate perioperative period, which provided satisfactory hemostatic control initially. We also elected to rest her knee with compression and bracing for the first postoperative week to further reduce the risk of hemarthrosis.

Despite data supporting the use of replacement products in the perioperative period, the particular selection of a replacement product remains controversial. Transfusion-associated complications may limit the use of FFP and cryo [2,21]. FFP is associated with acute lung injury and volume overload. Both cryo and FFP consist of many other plasma proteins in addition to fibrinogen including fibronectin, von Willebrand factor, factor VIII, factor XIII, and other potential anaphylatoxins putting patients at risk for allergic reactions [2]. Additionally, there is concern that the use of cryo poses a higher risk of viral transmission given the lack of virus inactivation during its preparation. Recently, the use of FC has gained more popularity.

Studies have shown FC to be equally effective in the treatment of afibrinogenemia when compared to cryo [2,19,21,22]. Distinct advantages of FC may include a better safety profile given the lack of aforementioned proteins and viral inactivation, as well as more accurate dosing and rapid administration. However, availability and increased costs have limited its use [21]. In our case, cryo was selected as an effective treatment choice.

Septic complications

Postoperative hemarthrosis is a key contributor to the development of deep joint infection. This has been well documented in the hemophiliac population undergoing TKA, with an overall infection rate of 7.9% [13]. Impaired hemostasis may impact the development of infection directly and indirectly [23]. A variety of postsurgical complications have been documented for patients with bleeding disorders including poor wound healing, increased transfusion requirements, and higher pain scores [23]. A recent article by Wong et al. [13] reported that hemophilia patients on a high clotting-factor replacement regime for the first two postoperative weeks had a substantially lower rate of prosthetic joint infections than patients who were maintained on the standard replacement guidelines from the World Federation of Hemophilia. Levels were measured and maintained at the time of surgery, 72 hours, 1 week, and 2 weeks postoperatively (2.15% vs 9.22%, $P = .005$).

In our patient, owing to the lack of close hematology follow-up, we failed to ensure that fibrinogen levels were appropriately maintained for postoperative healing beyond the first 72 hours after the TKA. The patient's fibrinogen levels likely descended below the target level after the inpatient stay. When considered in combination with her increased activity levels during therapy for her TKA, the lower fibrinogen levels may have contributed to the development of a postoperative hemarthrosis, thereby putting her at a theoretically higher risk for prosthetic joint infection.

Summary

We report a case in which a patient diagnosed with hypofibrinogenemia was successfully treated with a TKA. Despite efforts to manage this disorder perioperatively and limit the possibility of a hemarthrosis, the patient's postoperative course was complicated by an acute prosthetic joint infection. Patients with hypofibrinogenemia may often be asymptomatic without significant bleeding diathesis but are at risk of hemodynamic complications and postoperative infection; these risks are likely magnified when considering total joint arthroplasty.

Current controversies and future considerations

Although no guidelines currently exist for the surgical care of patients with these rare disorders, successful perioperative management of these patients may be possible by achieving and maintaining a target goal for the fibrinogen level >100 mg/dL at the time of surgery. This goal is based on clinical reasoning and prior literature and is subject to modification secondary to the severity of the deficiency and procedure invasiveness. Based on our experience, we would recommend routine assessment of fibrinogen levels postoperatively with the use of FFP, cryo, or FC transfusion to maintain the patient in the target range to decrease the risk of hemarthrosis or acute prosthetic joint infection. Preoperative consultation and perioperative comanagement with a hematologist is also an essential element of care for patients with these rare disorders. Further work is required including randomized controlled trials to determine the optimal postoperative testing and treatment regimen in orthopaedic patients.

KEY POINTS

- Important to inquire about a history or a family history of bleeding complications secondary to surgery.
- Any coagulation profile lab abnormalities should prompt a hematology consult pre-operatively.
- Extremely close follow-up is required of these patients post-operatively secondary to higher risk of complications.

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