Clinical Case Report

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A new perspective on perioperative coagulation management in a patient with congenital factor VII deficiency

A case report

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Abstract

Rationale: Congenital factor VII (FVII) deficiency is a rare coagulopathy. There are little clinical data for congenital FVII deficiency and no evidence-based medicine guidelines for treatment.

Patient concerns: A 48-year-old woman with gallbladder stones suffered from intermittent abdominal pain for 2 months that was accompanied by an abnormally prolonged prothrombin time.

Diagnoses: The woman was diagnosed as having cholecystolithiasis with cholecystitis and congenital FVII deficiency.

Intervention: Preoperative evaluation confirmed the necessity of recombinant activated factor VII (rFVIIa) replacement therapy. We monitored the plasma factor VII activity (FVII:C) and coagulation function, determined the half-life of rFVIIa in the patient, and administered personalized rFVIIa replacement therapy.

Outcomes: Laparoscopic cholecystectomy was performed successfully, and the patient recovered well without any complications.

Lessons: The clinical manifestations and severity of bleeding in patients with congenital FVII deficiency can vary widely. The history of massive bleeding and plasma FVII:C are the decisive factors when implementing a replacement therapy. The actual half-life of rFVIIa can be determined from intensive monitoring results of plasma FVII:C at the beginning of replacement therapy, which could further guide the personalization of rFVIIa replacement therapy.

Abbreviations: ECG = electrocardiograph, FVII:C = factor VII activity, FVII = factor VII, INR = international normalized ratio, PT = prothrombin time, rFVIIa = recombinant activated factor VII.

Keywords: bleeding disorders, factor VII deficiency, individual therapy, laparoscopic cholecystectomy, perioperative care

1. Introduction

Congenital factor VII (FVII) deficiency is a rare disease related to autosomal recessive disorder or FVII gene mutation, and can increase the risk of developing a massive hemorrhage.[1] The prevalence is approximately 1 in 500,000 individuals, and in 18% of patients, the disease can be related to inbreeding. Heterozygous patients are usually asymptomatic, whereas patients who are homozygous or homozygote complex heterozygote may develop bleeding symptoms.[2]

The severity of clinical manifestations in congenital FVII deficiency patients is extremally different, ranging from asymptomatic to life-threatening bleeding.[1,3,4] The treatment therapy is dependent on the clinical manifestations, and varies from no intervention to frequent FVII regimen administration. Recombinant activated FVII (rFVIIa) replacement is the most widely used therapeutic management for either spontaneous or surgical bleeding in these patients.[5]

At present, the optimal therapy for congenital FVII deficiency patients remains unclear, and there are few reports on real-time monitoring of plasma FVII levels that could guide the perioperative use of rFVIIa. Therefore, we provided a new perspective on perioperative coagulation management by reporting on the treatment process of a patient with congenital FVII deficiency undergoing laparoscopic cholecystectomy.

2. Case presentation

A 48-year-old woman had been diagnosed with cholelithiasis for 16 years. In the recent 2 months, the patient presented with symptoms of intermittent cholecystitis and decided to receive

Editor: N/A.

YS and LJ have contributed equally to this work.

Patient anonymity and informed consent: The patient has provided informed consent for publication of the case.

Consent for publication: Written informed consent for publication of clinical details and images were obtained from the patient.

The authors report no conflicts of interest.

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Medicine (2018) 97:44(e12776)

Received: 13 June 2018 / Accepted: 17 September 2018

http://dx.doi.org/10.1097/MD.0000000000012776

surgical treatment. However, the preoperative examination indicated an abnormally prolonged prothrombin time (PT) (data unknown). Then, the patient was transferred to the hematology department of our hospital. The examination of blood clotting function showed that PT was 29.8 seconds, international normalized ratio (INR) was 2.82, FVII:C was 3%, and FVII inhibitor activity was negative. Genetic analysis found a double heterozygous mutation on the FVII gene. Thromboelastography indicated that the comprehensive coagulation function was normal without any tendency for fibrinolysis. Therefore, the diagnosis of congenital FVII deficiency was confirmed. Abdominal ultrasound showed that the gallbladder wall was approximately 0.5 cm in thickness, and multiple gallstones were observed with the largest measuring 1.5 cm in diameter. Physical examination showed the height of the patient was 166 cm, weight was 90 kg, a mild tenderness was presented in the right epigastrium without rebound pain or muscular tension, and Murphy sign was positive. Thus, cholecystolithiasis with cholecystitis was diagnosed. An electrocardiograph (ECG) showed a complete right bundle branch block. Other preoperative examinations, including routine blood, liver and renal function tests, were all within normal ranges, and tests for hepatitis B and C were negative.

In regards to patient history, she received an appendectomy 16 years ago, without bleeding or any other complications. The patient had given birth to 2 children, and she suffered from a massive bleeding during her first delivery. In addition, the patient denied family history of similar diseases (2 sisters, 1 younger brother, and 2 sons; the FVII gene sequencing of relatives did not reveal any mutation), and her parents were not close relatives.

Based on the finding of moderately deficient FVII activity (FVII:C, 3%) and the history of massive bleeding during parturition, perioperative replacement therapy was necessary and rFVIIa (Recombinant Human Coagulation Factor VII for Injection, NovoSeven, Novo Nordisk A/S) was the first choice. After a multidisciplinary discussion, the perioperative replacement included 2 main strategies. First, the time points of plasma FVII:C monitoring, that is, 30 minutes before the operation, at the beginning of the operation, and 30 minutes later, then every hour for the first 6 hours after the operation, every 3 hours in the following 6 to 24 hours, and every 6 to 12 hours for 4 days after the operation. Second, rFVIIa replacement therapy, that is, the first dose of 30 μg/kg should be given at the time of first incision, then a dose of 10 μg/kg at 6 hours after the operation, a 30 μg/kg dose at 12 hours after operation, and a 10 to 20 μg/kg dose given every 6 to 12 hours until 4 days after the operation, according to the plasma FVII:C. If FVII:C is <20% or the patient shows a tendency to bleed, a temporary dose of rFVIIa should be given. For our patient, the dynamic results of plasma FVII:C, as well as the administration time and dose of rFVIIa, are summarized in Figure 1.

As a result of the careful preparation, laparoscopic cholecystectomy was performed successfully. The patient recovered well and was discharged on the fourth day following the operation without any complications, and no bleeding or thrombotic accidents occurred.

3. Discussion

The clinical evaluation of bleeding risk and perioperative management in patients with congenital FVII deficiency are diverse. In 2011, Benlakhal et al[6] suggested that the threshold level of plasma FVII:C was 10% for severe bleeding risk. However, in 2012, Sheth et al considered that there was a weak correlation between plasma FVII:C and the risk of bleeding; instead, the patient's personal and family history were much more important. As it was difficult to predict bleeding in the absence of these data, they suggested that the plasma FVII:C threshold level for significant bleeding risk should be 20%. Also, when personal or family history of bleeding was confirmed, there was still a high risk of excessive bleeding when plasma FVII:C was high.[7] In 2016, Sevenet et al and Woehrle et al[8,9] also found that the occurrence and severity of bleeding were not necessarily associated with plasma FVII:C, and the risk of

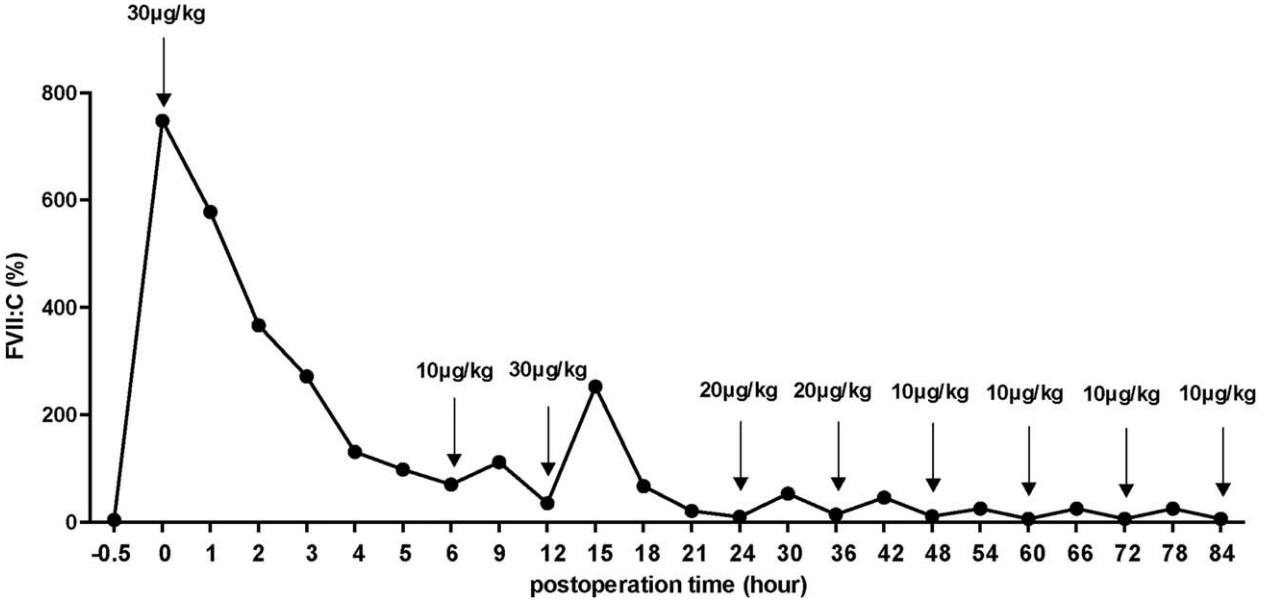

Figure 1. The dynamic results of plasma FVII:C and the administration time and dose of recombinant activated factor VII during the perioperative period. FVII:C = factor VII activity.

bleeding could not be accurately predicted by experimental results; the history of bleeding was a more reliable predictor for perioperative bleeding risk. In 2017, Di Minno et al came to the conclusion, by analyzing clinical data of 95 FVII deficiency patients (61 major operations and 49 minor operations) in the STER database, that a history of major bleeding was the only independent predictor of perioperative replacement therapy. As there was no recommended standard, rFVIIa replacement therapy varied greatly and 95.5% of FVII deficiency patients experienced a benefit and obtained competent haemostasis by receiving a low-dose (20 μg/kg) perioperative replacement. For patients with a high risk of bleeding, the same dosage was repeated up to 8 to 10 times. Additionally, for the patients without a history of bleeding, the single-dose replacement therapy was a good choice.[10]

In this case report, we consulted with hematologists and pharmacists closely, and monitored FVII:C, PT, INR, and other serological indicators during the replacement therapy. At the same time, we use the pharmacokinetic one-atrioventricular model, $C = Co*e^{-kt}$ (C: drug concentration *in vivo*, Co: drug concentration during initial administration) to calculate the actual half-life (t1/2) of rFVIIa in this patient. According to the plasma FVII:C in the first 6 hours of replacement therapy, we simulated that $K = 0.435$. Therefore, the t1/2 of rFVIIa in this patient was 1.59 hours ($t1/2 = 0.693/k = 1.59$ hours), which provided a basis for the subsequent administration schedule. Based on the above results, we speculated the dosage and interval of rFVIIa and gave the patient a personalized replacement therapy regimen according to the plasma FVII:C. The patient recovered well without any complications.

At present, whether rFVIIa replacement therapy can pose the risk of thrombosis in congenitally FVII deficiency patients is unknown.[11] However, based on the propensity for thrombotic complications in other situations, the use of rFVIIa should be given careful attention.[12] To lower the risk of bleeding without increasing thrombotic complications, it is necessary to consider the half-life and real metabolism of rFVIIa in each individual patient. Therefore, the future trend of rFVIIa replacement therapy in congenital FVII deficiency patients may develop into personalized treatment.

4. Conclusion

As a rare coagulation dysfunction disease, not all patients with congenital FVII deficiency need rFVIIa replacement therapy when they undergo invasive procedures. A history of massive bleeding and the level of plasma FVII:C are the indispensable decisive factors. For patients in need of replacement therapy, surgeons in cooperation with hematologists and pharmacists can determine the actual drug metabolism in each individual from the intensive monitoring results of plasma FVII:C at the beginning of replacement therapy on onwards to formulate a reasonable and economical individualized replacement scheme. This case report provides valuable data and a new perspective on perioperative coagulation management in patients with congenital FVII deficiency.

Acknowledgment

The authors thank the laboratory technician at the Hematology Department for their excellent work on the assay of plasma FVII:C.

Author contributions

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