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Severe Congenital Factor VII Deficiency with Normal Perioperative Coagulation Profile Based on ROTEM Analysis in a Hepatectomy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEF 1 Richard S. Yeom
EF 2 Xuejun A. Wang
EF 1 Elia Elia
EF 1 Uzung Yoon

1 Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA
2 Department of Internal Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Corresponding Author: Richard S. Yeom, e-mail: Richard.yeom@jefferson.edu
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Patient: Female, 21-year-old
Final Diagnosis: Congenital factor VII deficiency
Symptoms: Coagulopathy • radial artery thrombosis
Medication: —
Clinical Procedure: —
Specialty: Anesthesiology • Hematology

Objective: Rare disease

Background: Factor VII (FVII) deficiency is the most common autosomal-recessive bleeding disorder. FVII activity level (FVII: C) of 10-20% is often used as the threshold for administering activated recombinant FVII (rFVIIa) for patients undergoing major surgery. However, rFVIIa is expensive and carries the risk of a thromboembolic event, and thus should only be administered when truly indicated.

Case Report: A 22-year-old woman with 8% FVII: C underwent a hepatectomy. Although there were no clinical signs of bleeding, peri-operative administration of rFVIIa was recommended by the hematologist (first dose at surgical incision, then 4 h later, then every 12 h until 48 h postoperatively). Intraoperatively, serials of ROTEM analysis were performed to evaluate the effect of rFVIIa administration. No significant effect of rFVIIa was seen on NATEM. Surgery was unremarkable, without any significant blood loss. The patient developed radial artery thrombosis 24 h postoperatively, the arterial line was removed, and rFVIIa was discontinued (PT: 14.6, FVII: C 36%). On POD 3, INR was elevated (3.15, FVII: C 3%). To correct INR, the patient was transfused 8 units of FFP, despite any signs of clinical bleeding. However, INR and FVII: C did not correct and the patient was discharged on POD 7 in a stable condition.

Conclusions: Even with FVII: C of 8%, the ROTEM analysis revealed a normal coagulation status. The administration of rFVIIa did not improve the already normal baseline coagulation profile, but rather potentially led to an accelerated coagulation or hypercoagulable state and may have led to the radial artery thrombosis. We endorse the use of viscoelastic testing for hemostasis assessment and factor replacement in congenital FVII deficiency.

Keywords: Factor VII Deficiency • Factor VIIa • Hepatectomy • Thrombelastography • Blood Coagulation Disorders

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Background

The body controls bleeding by means of a finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic activities [1]. Any deficiency along this hemostasis pathway can alter coagulability and have clinical consequences. In particular, a deficiency of factor VII (FVII), which plays a crucial role in the hemostasis pathway by initiating the extrinsic coagulation cascade, can lead to spontaneous bleeding.

FVII deficiency is the most common autosomal-recessive bleeding disorder and affects up to 1 in 300 000 people worldwide [2]. In the event of an endothelial injury, individuals with FVII deficiency are unable to mount the coagulation cascade effectively because it requires the activated form of FVII (FVIIa), which binds to the tissue factor (TF) to form a FVIIa-TF complex, and in turn activates factors IX to IXa, and X to Xa, leading to the promotion of fibrin clot formation further along the coagulation cascade [3].

No clear perioperative guidelines exist for patients with FVII deficiency undergoing major surgery. A retrospective analysis performed by Benlakhal et al suggested using 10% FVII procoagulant activity level (FVII: C) as the threshold for administering recombinant FVIIa (rFVIIa) for patients undergoing major surgery [4]. Bauer demonstrated that restoring FVII levels to 15-20% of normal is usually adequate to control bleeding [5].

The treatment of FVII deficiency includes the administration of fresh-frozen plasma (FFP) or FVII concentrate. The cost for the concentrate is, however, exceedingly high ($2.15 per 1 mcg, which amounts to $4300 for a single dose of 2000 mcg), and it carries the risk of thromboembolic events [6]. Thus, it should only be administered when truly indicated.

To decide whether to administer rFVIIa, physicians often rely on plasma-derived laboratory values such as FVII: C or international normalized ratio (INR). However, these plasma-derived laboratory values may not always correlate with the real coagulation status of the patient or predict the risk of bleeding in invasive procedures. Perioperative substitution therapy with rFVIIa may not be indicated, even when FVII levels are low, if the patient does not have a history of significant hemorrhagic episodes.

In this case report, we demonstrate that rotational thromboelastometry (ROTEM® Delta Instrumentation Laboratory Co., Bedford, MA, USA) can provide a new way to guide perioperative factor replacement therapy in patients with congenital FVII deficiency.

ROTEM® assesses clot formation, kinetics, strength, and dissolution by measuring and displaying the amount of a continuously applied rotational force that is transmitted to an electromechanical transduction system by developing clot. A cylindrical cup containing a 340-µl whole-blood sample remains fixed while a pin suspended on a ball-bearing mechanism initially oscillates through 4° 75' every 6 s through application of a constant force. As the viscoelastic strength of the clot increases, the rotation of the pin is impeded and is detected optically using a charge-coupled device image sensor system. The system records the kinetic changes in a sample of citrated whole blood during clot initiation, propagation, stabilization, and lysis. The NATEM (non-activated rotational thromboelastometry) is a particular test of ROTEM® that does not contain any activators and evaluates both intrinsic and extrinsic pathways of whole-blood coagulation.

Case Report

A 22-year-old woman with congenital FVII deficiency underwent segment 5 and 6 hepatectomy for a bleeding hepatic adenoma. Preoperative work-up revealed prothrombin time (PT) of 32.4, the INR of 2.88, and FVII: C of 8%. Her full hematology work-up showed isolated FVll deficiency, with normal levels of all other coagulation factors.

Despite this elevated INR and low activity level, the patient did not have any history of easy bruising or any other signs of frequent or severe bleeding. A detailed history-taking and physical exam is crucial in factor deficiency patients since there is no relationship between the FVII plasma level and clinical manifestations. Prior to the procedure, the patient saw a hematologist, who recommended the administration of rFVIIa 2000 mcg prior to the incision, with the repeat dosing 4 h after the initial dose, and every 12 h thereafter until 48 h postoperatively. This decision was based on the current literature suggesting to restore FVII levels to 10-20% for major surgery with potential of significant blood loss.

Following an unremarkable induction of anesthesia, a left radial arterial line was placed to enable close hemodynamic monitoring and frequent blood sampling. To assess the baseline coagulation status of the patient, a NATEM assay was performed prior to the administration of rFVIIa to assess the baseline coagulation status of the patient, and the result was normal (**Figure 1**). At 10 min prior to the incision, the patient received rFVIIa, and NATEM was repeated 30 min and 120 min after administration. At both points in time, NATEM did not show any significant changes compared to the baseline NATEM seen in **Figure 1.** A repeat dose of rFVIIa was administered 4 h following the initial dose. Repeat NATEMs were done 120 min and 210 min after the repeat dose of rFVIIa, and again they did not show any significant change. The surgery proceeded as expected without any significant blood loss, and the patient

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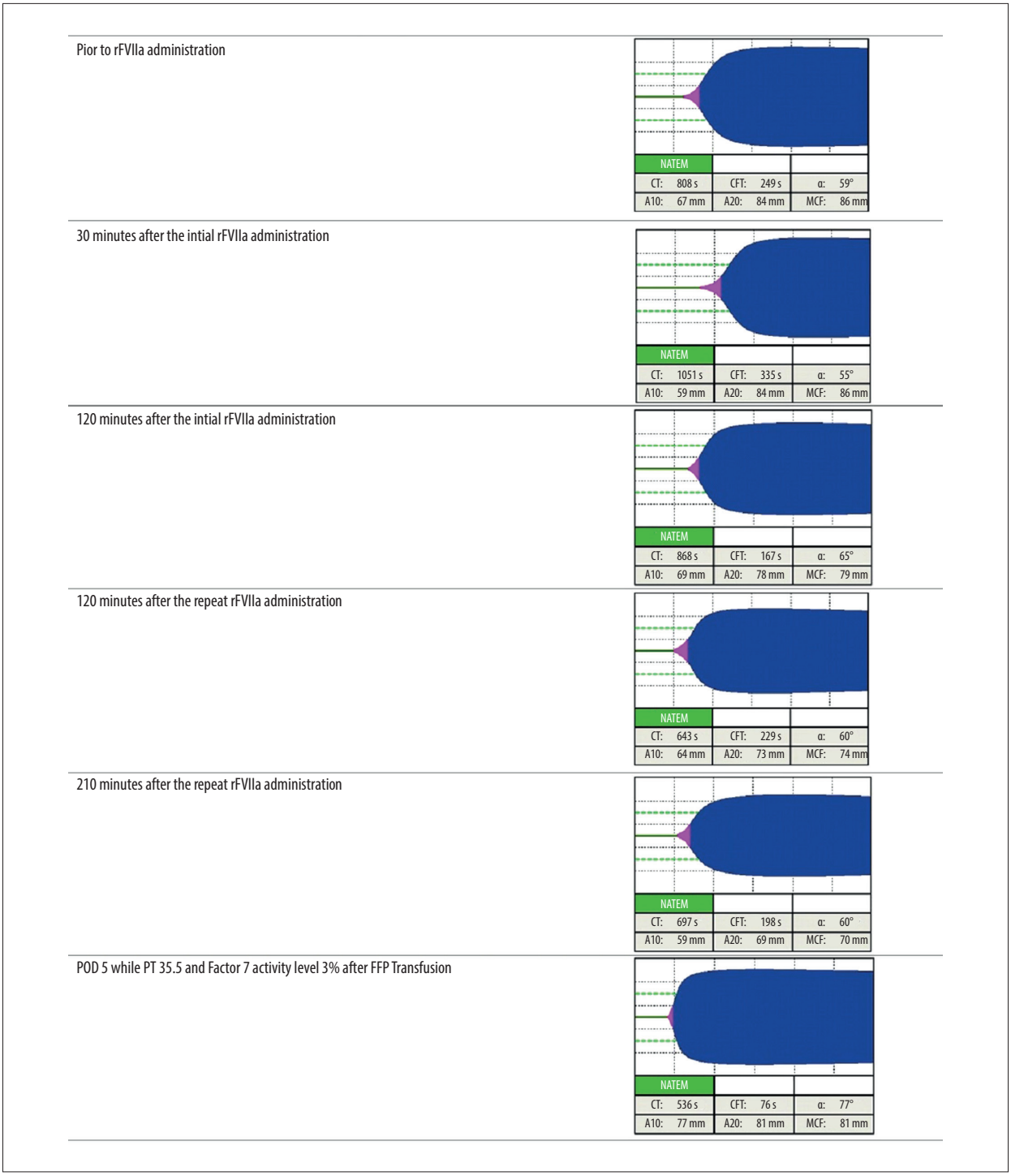

Figure 1. Non-Activated thromboelastometry (NATEM) analysis results during the perioperative period. Note the normal NATEM prior to any administration of rFVIIa despite FVII procoagulant activity level (FVII: C) of 8%.

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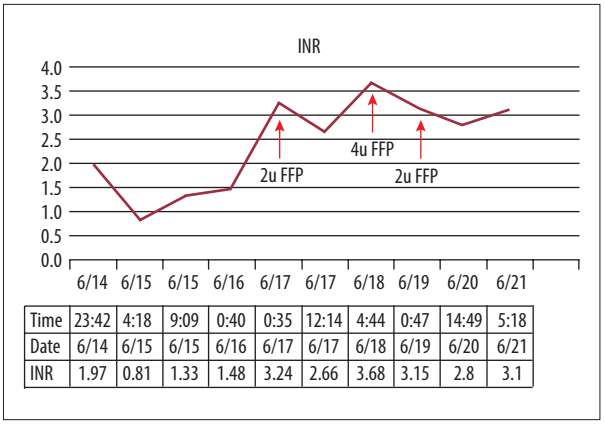

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Date	6/14	6/15	6/15	6/16	6/17	6/17	6/18	6/19	6/20	6/21
INR	1.97	0.81	1.33	1.48	3.24	2.66	3.68	3.15	2.8	3.1

Figure 2. INR results and FFP transfusion during the perioperative period. Note the elevated INR despite transfusion of 8 units of FFP in the absence of bleeding.

was transferred to the floor following an unremarkable course in the Postoperative Anesthesia Recovery Unit (PACU).

At 24 h postoperatively, after the patient had received 4 doses of rFVIIa (2 doses intraoperatively and 2 doses postoperatively), she developed left radial artery thrombosis at the site of the left radial arterial line. In the setting of new arterial thrombosis, the arterial line was discontinued and the remaining scheduled rFVIIa administration was discontinued. At this time, the patient's PT was 14.6 and the FVII: C was 36%, and the patient did not demonstrate any clinical signs of bleeding.

The patient's postoperative course was further complicated by a sudden elevation of PT and INR on postoperative day (POD) 3. The PT was elevated to 36.5, the INR was elevated to 3.24, and the FVII: C had decreased to 3%. Despite the changes in laboratory values, the patient did not demonstrate any clinical signs of bleeding.

To correct for the low FVII: C and the elevated PT and INR, a total of 8 units of fresh-frozen plasma (FFP) was administered throughout POD 3 to 5; however, the PT remained elevated in the 30's, INR range was 2.6-3.6, and the FVII: C was unchanged at 3% in multiple repeat measurements (**Figure 2**). On POD 5, the FFP transfusion was discontinued given that the hemoglobin had been stable and the PT and FVII: C level remained unchanged. A repeat NATEM done at this time showed decreased clotting time (CT) and increased maximum clot firmness (MCF) compared to the baseline NATEM (**Figure 1**).

On POD 6, the patient was re-started on rFVIIa. After 2 additional doses of rFVIIa for a total of 6 doses of rFVIIa during the admission, on POD 7 the patient was discharged with an outpatient follow-up. The PT and the INR on the day of discharge were still elevated at 34.9, and 3.10, respectively; however, the patient did not demonstrate any bleeding, and was stable for the discharge. At 1-month follow-up, patient's INR remained elevated at 3.0, but the patient did not exhibit any symptoms of easy bruising or bleeding without any hemostatic support.

Discussion

The primary finding in this case is that even with a FVII: C of 8%, which could have resulted in an increased risk of bleeding during the hepatectomy, the patient's clinical coagulation status was normal based on ROTEM analysis. Additionally, the administration of rFVIIa possibly may have led to a hypercoagulation state and the subsequent radial artery thrombosis. The rapid drop in factor VII between POD 1 and POD 3 can be explained by the short half-life of factor VII of approximately 3-6 h and the complex formation of rFVIIa with plasma protease inhibitor, primarily antithrombin III. The circulation complex is then cleared by the liver and further processed and excreted [7]. Postoperatively, INR remained elevated despite transfusion of FFP and rFVIIa administration due to the remaining FVII: C deficit. The highest measured FVIIa level was 36%.

Plasma FVII is a vitamin K-dependent zymogen with a short half-life of up to 3-6 h. Even though FVII activity below 8-10% is likely to result in bleeding symptoms, the clinical presentations of FVII deficiency can vary significantly among affected patients, ranging from having no spontaneous bleeding to having repeated life-threatening bleeding complications [8].

A major reason for the discrepancy between low FVII activity and the lack of bleeding may be variable individual sensitivities to TF. Some FVII variants give erroneous quantitation when using TF derived from oxen or rabbits, but have demonstrated more accurate activity in the presence of human TF [8]. The majority of patients with FVII deficiency have quantitative defects, with decreased FVII: C and normal FVII antigen (FVII: Ag). However, it is not uncommon to observe qualitative defects, with both decreased FVII: C and decreased FVII: Ag, partly as a result of reagents to FVII variants [9].

A decreased FVII: C due to congenital FVII deficiency will lead to an elevated PT and INR value. Other tests, including activated partial thromboplastin time (aPTT), thrombin time (TT), platelets, and fibrinogen concentration, remain within normal limits. However, an elevated PT and INR value only reflects a dysfunction or decreased production of the coagulation factors in the extrinsic pathway, and not necessarily a bleeding risk. This is especially true for FVII deficiency, since FVII has the shortest half-life out of all procoagulant factors, approximately 3-6 h [10]. Importantly, a dysfunction of a single or multiple coagulant factors does not necessarily translate into a dysfunction of hemostasis, because an adequate hemostasis does

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not require 100% of all coagulation factors [11]. Therefore, in general, the plasma-derived laboratory parameters are not a good indicator to assess the risk for bleeding.

Intraoperatively, hepatectomy presents a unique risk of alteration in coagulation. First, significant blood loss during a hepatectomy can lead to consumption coagulopathy. Second, synthetic function of the liver may be compromised depending on the size of resection, resulting in coagulopathy. Intra- and postoperative alterations of coagulation after a hepatectomy are difficult to predict since the lobe, size of resection and blood loss are variable case by case. Studies have shown that conventionally used coagulation tests like PT, PTT, INR do not correlate with viscoelastic testing in hepatectomies [12-15]. The combination of routine coagulation monitoring and ROTEM® analyses may provide a more complete picture of the coagulation status.

Successful cardiac surgery with congenital FVII deficiency and without preoperative rFVIIa replacement has been reported in the literature. Syburra et al reported a mitral valve surgery where no preoperative rFVIIa was given because the patient had no previous bleeding incident despite severe FVII deficiency (<2%; INR 3.9). Intraoperatively, 1800 IU of plasma-derived FVII was administered before heparin neutralization. FVII: C was increased from 3% to 36%, and it remained at 15-20% in the following 12 h. An additional 600 IU of plasma-derived FVII was repeated twice at 12-h intervals. No serious bleeding was reported after stopping FVII replacement despite plasma FVII activity of 2%-5% (INR 4.6-5.0) [16]. This is very similar to our case, where low FVII: C was not associated with clinical bleeding in the perioperative period.

There is no clear evidence that prophylactic administration of rFVIIa and FFP improves outcomes when it is used solely to correct INR in patients with lab abnormalities without clinical bleeding [17]. Furthermore, rFVIIa can cause a hypercoagulable state and therefore increase the risk of thrombosis. Similarly, FFP transfusion has a potential to cause a volume overloaded state, hypersensitivity reaction, and transfusion reaction, which all can result in longer hospital course.

The recent evidence has indicated that viscoelastic tests of coagulation, such as ROTEM, offer better clinical utility in assessing hemostatic function in patients with congenital factor deficiency compared to the INR [18]. This is because the ROTEM is analyzed from the whole-blood sample and evaluates the kinetics and coagulation from the initial clot formation to the final clot strength. This allows for a much more comprehensive picture of coagulation status, capturing the importance of plasma, blood cells, and platelets during hemostasis.

In contrast, the INR is analyzed from isolated plasma, and its value is generated at the initiation of fibrin polymerization [19]. The INR only considers the procoagulant levels, especially for FVII, and is unable to measure the compensatory effect of the intrinsic and common pathway, platelet interaction, and fibrinogen.

In our case, a NATEM assay was chosen to avoid iatrogenic activation of coagulation by activators contained in the reagent solution. EXTEM contains the activator tissue factor and INTEM contains ellagic acid. NATEM only reverses the citrate contained in the collection tubing with calcium without adding any activators. Reference values were validated by the institutional anesthesia coagulation laboratory.

Most anesthesiologists familiar with viscoelastic testing will recognize that INR is not truly reflective of clinical coagulation status nor is it an indication for FFP transfusion or the assessment for the risk of bleeding. However, FVII: C less than 8% is not commonly seen and would generally lead physicians to choose to administer rFVIIa or transfuse FFP prior to an invasive procedure due to the fear of spontaneous bleeding. Regardless of the results of laboratory tests, however, if there is no bleeding, the blood products are not indicated prophylactically based on the Practice Guidelines for Perioperative Blood Management from the American Society of Anesthesiologists in 2015 [20].

Physicians should be encouraged to utilize viscoelastic assays to assess the bleeding risks and to guide factor replacement therapy. Multiple studies have shown that thromboelastography-guided transfusion decreased transfusions of FFP, administration of factor concentrates, and intraoperative blood loss and was superior to conventional coagulation tests [18,21]. Currently, there are no official guidelines to use viscoelastic testing for hemostatic assessment in congenital factor deficiency and it should be considered on a case-by-case basis and clinical experience.

Conclusions

When evaluating patients with congenital factor deficiency, even those with an extremely low FVII: C level do not necessarily have abnormal clinical coagulation based on ROTEM analysis. In our case, the administration of rFVIIa did not improve the baseline coagulation profile, but rather led to a hypercoagulable profile that possibly may have resulted in the radial artery thrombosis. Therefore, we encourage the use of viscoelasticity such as ROTEM for hemostasis assessment and factor replacement in congenital factor deficiency.

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Department and Institution Where Work Was Done

Department of Anesthesiology at Thomas Jefferson University Hospital, Philadelphia, PA.

Conflicts of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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