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CLINICAL REPORT

Postsurgical coagulopathy in a hemophilia A patient with inhibitors: efficacy of recombinant factor VIIa

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Abstract Perioperative hemostatic management in patients with hemophilia A who develop the coagulation factor VIII (FVIII) inhibitor is challenging, because exogenous FVIII is neutralized, which boosts the inhibitor to provoke postoperative coagulopathy. Recombinant activated factor VII (rFVIIa) has become available for this type of patient, although FVIII is sometimes required. We treated a 56-year-old male patient with hemophilia A with FVIII inhibitor scheduled for total hip arthroplasty (THA) and total knee arthroplasty (TKA). We used rFVIIa for THA; however, the amount of bleeding was 2,500 ml and blood transfusion was required, which boosted FVIII inhibitor after surgery. The TKA was then scheduled for 19 months later, after the level of the inhibitor had reduced to the preoperative level. Unfortunately, rFVIIa failed to improve PT/APTT, and thus we used recombinant factor VIII (rFVIII). The amount of bleeding during TKA was 1,340 ml, while the level of the inhibitor increased to a greater level than that after THA, provoking uncontrollable bleeding. For anesthetic management in hemophilia A patients with FVIII inhibitor, anesthesiologists must pay attention to postoperative coagulopathy, and every effort should be used to minimize exposure to FVIII. Furthermore, when rFVIIa is ineffective, postponement of surgery until rFVIIa regains its efficacy may be beneficial as compared to an operation with FVIII.

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Introduction

Hemophilia A is characterized by a functional deficiency of coagulation factor VIII (FVIII), which leads to bleeding in joints, muscles, and soft tissues. Although replacement therapy with FVIII is commonly used, a blood-borne viral infection occurs and in about 25 % of treated patients FVIII inhibitor develops to render standard replacement therapy ineffective [1]. Such a blood-borne viral infection can be reduced by use of a recombinant product of FVIII (rFVIII, Kogenate; Bayer, Leverkusen, Germany), although development of the inhibitor is not avoidable [2].

Recombinant activated factor VII (rFVIIa, Novo Seven; Novo Nordisk, Bagsvaerd, Denmark) is an alternative for rFVIII as it does not provoke production of FVIII inhibitor and has been reported to be potent and safe as so-called bypass therapy. Therefore, rFVIIa is used as first-line therapy in surgery for this type of the patient [3–5]. However, in cases in which rFVIIa fails to improve hemostasis, rescue with rFVIII, known as neutralizing therapy, can be used [6]. The drawback with use of rFVIII is an increased level of the inhibitor, which can provoke coagulopathy, thereby affecting the scheduling of surgical procedures [2].

In this article, we describe hemostatic management for two orthopedic surgeries performed in the same patient with hemophilia A, who developed FVIII inhibitor. Although we planned to use rFVIIa, other coagulation factors containing FVIII were required to secure hemostasis, which provoked uncontrollable postoperative coagulopathy.

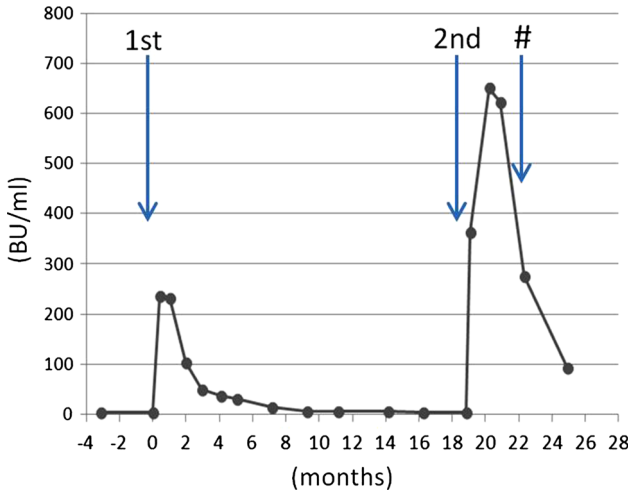

Fig. 1 Time course of inhibitor levels during perioperative period. The increase in the inhibitor was greater and lasted longer after the second operation (*2nd*) with recombinant factor VII (rFVIII) than after the first operation (*1st*) with recombinant factor VIIa (rFVIIa). # Bleeding episode

Case report

The patient was a 56-year-old man (weight 56 kg, height 168 cm) who had been diagnosed with hemophilia A at the age of 20 years and had received infusions of nonheated plasma-derived factor VIII when required for bleeding episodes. The inhibitor was detected when the patient was 43 years old, when he was also diagnosed as positive for hepatitis C virus and for the human immunodeficiency virus. At the age of 51 years, the patient began to receive rFVIIa instead of nonheated plasma-derived FVIII. Difficulty in walking from hemophilic arthropathy in the right hip joint and knee developed, and he was scheduled for total hip arthroplasty (THA) followed by total knee arthroplasty (TKA) procedures.

First operation

A physical examination revealed normal findings, except for gait impairment, and peripheral blood examination findings were also normal. In a hemostatic examination, the FVIII activity level was 2 % and the inhibitor was 4–10 Bethesda units/ml (BU/ml). Prothrombin time (PT-INR) and activated partial thromboplastin time (APTT) were both impaired, but improved with 9.6 mg rFVIIa (1.29–0.44 and 103–42.8 s, respectively). Because of the improvement in PT-INR/APTT by rFVIIa and high titer of the inhibitor, we planned to administer 9.6 mg rFVIIa just before anesthesia induction and repeat every 2 h during surgery until postoperative day (POD) 2 as bypass therapy [3–5].

Anesthesia was induced with thiamylal, vecuronium, and fentanyl, and maintained with sevoflurane and fentanyl. After supplementation with rFVIIa just before surgery, PT-INR, APTT, and fibrinogen were 0.48, 50.9 s, and 169.5 mg/dl, respectively. As bleeding increased, fibrinogen became depleted (87.3 mg/dl) whereas PT-INR and APTT were maintained (0.61 and 54.8 s, respectively). Therefore, we transfused 320 ml fresh frozen plasma, 2 g fibrinogen, and 1,200 ml red blood cells. Surgery ended without complications, except for 2,500 ml of bleeding. After the operation, rFVIIa was repeatedly given in decremental steps until POD5.

Postsurgical bleeding was minimal and no adverse effects were observed; the patient was discharged on POD46. The cost of hemostatic agent administration from the operation until POD4 was approximately 180,000 $US. The titer of the inhibitor was increased (233 BU/ml at 1 month, 30 BU/ml at 5 months after surgery) (Fig. 1), which required more than 18 months to return to the preoperation level.

Second operation

Nineteen months after the first operation, when the inhibitor had returned to a low level (3 BU/ml), TKA was scheduled. However, at that time, FVIII coagulant activity was <1 % and APTT was extremely increased (>240 s) although PT-INR remained at the same level as before the first operation (1.25). Administration of rFVIIa was less effective than with the first procedure (PT-INR 1.25–0.79, APTT >240 to >240 s, respectively). Thus, based on the guideline (Japanese Society on Thrombosis and Hemostasis, 2008) we decided to apply neutralization therapy with rFVIII instead of bypass therapy with rFVIIa [1, 6].

Anesthesia was performed in a similar manner as in the first operation. For hemostatic management, a bolus dose of rFVIII (8,000 U, i.v.), which was more than needed to neutralize the inhibitor, was given just before anesthesia induction, followed by a continuous infusion (400 U/h). PT-INR, APTT, and fibrinogen before surgery were 1.36, 53.9 s, and 173.1 mg/dl, respectively. The operation was performed using a thigh tourniquet, and VIII coagulant activity level and APTT were maintained during the procedure (87–109 %, 39.9–53.9 s, respectively). The amount of bleeding during the operation was 370 g and that after surgery was 970 g. On POD5, we converted from hemostatic management with rFVIII to rFVIIa, as the effect of FVIII was attenuated by an increase in the inhibitor after FVIII exposure.

The postsurgical course was uneventful and the patient was discharged on POD54. The cost of hemostatic administration from the operation until POD4 was approximately 38,500 $US. The increase in level of the

inhibitor was higher and longer than that after the first operation (651 BU/ml at 1 month, 93 BU/ml at 5 months after surgery) (Fig. 1), whereas APTT remained above the measureable limit (>240 s). Three months after the second operation, the patient suffered from uncontrollable hematemesis, which continued for several months, and was diagnosed with advanced hepatocellular carcinoma at 5 months. Six months after the operation, he was admitted because of hemorrhagic shock with massive hematemesis and treated with palliative therapy starting at 7 months. One year after the operation, the patient died of hepatic failure.

Discussion

The factor VIII inhibitor develops after exposure to exogenous FVIII, which in turn interferes with hemostatic therapy by neutralizing FVIII and accelerating its clearance to increase the risk for uncontrolled bleeding. Thus, rFVIIa is a primary option in patients with hemophilia A who develop the FVIII inhibitor [1, 3–5]. The strategy for perioperative hemostatic management in patients with hemophilia A who develop FVIII inhibitor varies based on the current titer for FVIII inhibitor, response to previous FVIII exposure, and estimated bleeding [6]. Response to rFVIIa should also be evaluated, as hemostatic management is not always accomplished with rFVIIa alone [7]. When rFVIIa is ineffective, other coagulation factors including FVIII are required. In the present case, various blood products containing FVIII as well as authentic FVIII were used. However, postoperative coagulopathy was not avoidable in either operation, especially after management with rFVIII, and uncontrollable bleeding occurred.

Our experience indicates that every effort to minimize exposure to FVIII should be made before administration of blood transfusion products containing FVIII. In the present case, we used rFVIII instead of rFVIIa, because the effect had decreased. Hayashi et al. [8] reported that the decreased effect of coagulation factors such as rFVIIa by long-term use may be regained by their discontinuation. Although the mechanism underlying this is not clear, administration of FVIII might be avoided by postponement of the second operation along with discontinuation of rFVIIa until the effect is regained.

During the operation, every attempt to reduce surgical bleeding, including use of a tourniquet, hypotension induction, and bone wax application, should be attempted [9–12]. When blood transfusion is required, use of a cell-salvaging system, absolute red blood cells, or coagulation factors other than FVIII may be primary options. If blood components containing FVIII (e.g., red blood cells, frozen fresh plasma) are needed, they should be given at the minimum required units. Avoiding FVIII is especially important for patients in whom multiple operations are scheduled, as postoperative coagulopathy compromises scheduling and hemostatic management following surgery. Thus, we recommend that the operation with the lower estimated amount of bleeding should be performed first.

The cost of rFVIIa also has great impact, even though it provides a high quality of life for hemophilia patients in both physiological and mental aspects [13]. In the present case, the cost for blood products required during the perioperative period (operation to POD4) was higher with rFVIIa-based management than with rFVIII-based hemostatic management by nearly 150,000 $US. However, because hemophilic patients have multiple arthropathies to be considered, the use of rFVIIa is thought to be relevant in view of the potential for uncontrollable and fatal bleeding [13]. Thus, close consultation with a hematologist is required for planning of perioperative hemostasis especially for hemophilia A patients, who possess FVIII inhibitor.

In conclusion, we performed perioperative hemostatic management for a patient with hemophilia A with the FVIII inhibitor. Although we used rFVIIa, other blood components including rFVIII were also required, resulting in uncontrollable and fatal bleeding. To avoid postoperative coagulopathy, every effort to reduce surgical bleeding must be considered. If multiple surgeries are scheduled, the operation with the lower amount of estimated bleeding should be performed first. Furthermore, when the effect of rFVIIa is reduced, postponement of the next surgery until rFVIIa regains its effect is also recommended.

Acknowledgments Publication of this case report was approved by the patient, who wished to provide information to promote a deeper understanding of hemophilia patients. (The patient died after the second operation.) The costs of hemostatic agent for each operations were calculated from Drug Price Standard in Japan before 2009, when the price of Novoseven increased.

Conflict of interest Noboru Saeki, Saya Mochizuki, Teruhisa Fujii, and Masashi Kawamoto have no conflicts of interest to declare.

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