

Gene therapy and cardiac surgery in a patient with hemophilia



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Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication May 28, 2022; revisions received July 31, 2022; accepted for publication Aug 8, 2022; available ahead of print Sept 22, 2022.

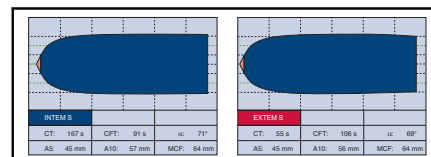
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JTCVS Techniques 2022;16:102-4

2666-2507

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<https://doi.org/10.1016/j.jtc.2022.08.028>



Results of rotational thromboelastography.

CENTRAL MESSAGE

We performed cardiac surgery safely on a patient with severe hemophilia A who had previously received gene therapy. A team-work approach is essential to achieve optimal results.

Hemophilia A is an X-linked bleeding disorder resulting from a deficiency of blood coagulation factor VIII (FVIII). The disease results in various degrees of FVIII deficiency. In hemophilia A, the factor level of <1% is classified as severe, 1% to 5% as moderate, and >5% as mild.¹ With improvements in care, the life expectancy of patients with hemophilia has increased.¹⁻³ As a consequence, more patients with hemophilia are encountering age-related comorbidities that may need cardiac surgery.¹⁻³ However, cardiac surgery is extremely challenging for them because of the increased bleeding risk.^{1,2}

Currently, gene therapy is an advanced therapy because it offers the potential for a cure through the endogenous production of coagulation factor or a reduced need for additional coagulation factor–replacement therapy.⁴ We present a patient with severe hemophilia A who had received gene therapy and who subsequently underwent on-pump coronary artery bypass grafts (CABGs) safely by correcting the coagulopathy using a lower total dose of FVIII replacement. This is the first report of a successful CABG surgery in a patient who had received gene therapy for severe hemophilia A.

METHODS

Patient Characteristics

A 60-year-old man was diagnosed with severe hemophilia A during childhood. Prophylactic therapy with FVIII concentrate was started at the age of 37 years. He received gene therapy in October 2019. He was

diagnosed to as having coronary artery disease with the initial symptoms of dyspnea on exertion. Findings of a coronary angiogram demonstrated triple vessel coronary artery disease (CAD-III), and the SYNTAX score was 43. After comprehensive discussion, the patient decided to receive CABG surgery. The patient signs informed consent for the publication of study data. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CE22221A) at May 19, 2022.

Surgical Procedures

On-pump CABG surgery was performed through a full sternotomy. The great saphenous vein was chosen as a conduit. Heparin was given before and during the cardiopulmonary bypass in order to achieve an activated clotting time greater than 400 seconds. During operation, tranexamic acid was given with continuous drip of 200 mg/h for 10 hours. The total aortic crossclamping time was 124 minutes, and the total bypass time was 166 minutes. Four coronary artery bypass graft (CABG-4) was performed uneventfully.

Replacement of Factor Concentrates

Hemostasis treatment was conducted in cooperation with a comprehensive multidisciplinary hemophilia team during the perioperative period. The level of FVIII was 36% when the patient received preoperative preparation. Examination of rotational thromboelastography was performed before systemic heparinization for the CPB. One loading dose of 4000 IU recombinant factor VIII (rFVIII; Kovaltry, 50 IU/kg [Bayer HealthCare]) was administered preoperatively, and a bolus of 3000 IU (37.5 IU/kg) was given 4 hours after the surgery. The operation was completed within 6 hours. Then, 4000 IU of rFVIII (50 IU/kg) was given every 8 hours on postoperative days (PODs) 1 and 2 to keep the trough level of FVIII above 80%. A dose of 4000 IU rFVIII (50 IU/kg) was given on POD 3. A dose of 3000 IU rFVIII (37.5 IU/kg) was then given on POD 4 and 5 to maintain a trough level above 60%. The series of FVIII level is shown in Figure 1.

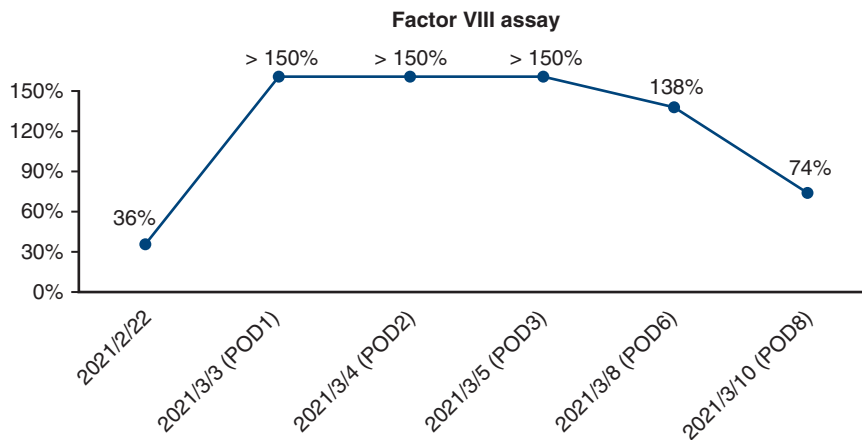


FIGURE 1. The series of factor VIII level during hospitalization. *POD*, Postoperative day.

RESULTS

The parameters of rotational thromboelastography were in the normal range (Figure 2). The estimated blood loss was 900 mL during the operation. The patient received 2 units (300 mL) of packed red blood cells, 6 units (600 mL) of fresh-frozen plasma, and 2 units (320 mL) of single-donor platelets intraoperatively.

The blood loss at 4 hours and 8 hours postoperatively was 480 mL and 500 mL, respectively. This is comparable with the drain output from our patients without hereditary bleeding disorders (HBDs) who received CABG. The mean drain volumes in these patients were 435 mL at 4 hours and 571 mL at 8 hours.

The endotracheal tube was removed on POD 1. The antiplatelet drug, acetyl salicylic acid 100 mg, was

given starting on POD 1. The patient was transferred to an ordinary ward on POD 4 and discharged on POD 8 uneventfully.

DISCUSSION

Cardiac surgery is an extreme challenge for patients with hemophilia. Coagulopathy caused by heparinization, cardiopulmonary bypass, hypothermia, sternotomy, and postoperative thromboprophylaxis raise the intra- and postoperative bleeding risk.^{1,2}

Replacement of the deficient coagulation factor is usually the cornerstone of treatment. The advent of rFVIII has eliminated the infective risk associated with factor concentrates, such as fresh frozen plasma.⁴ However, the relatively short half-life of FVIII in the circulation requires frequent

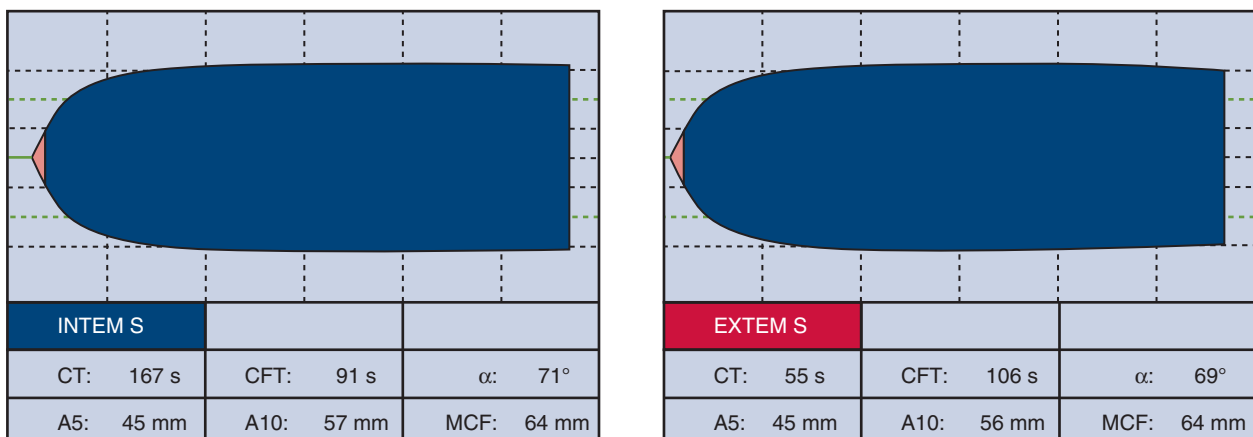


FIGURE 2. The results of rotational thromboelastography. Reference ranges of INTEM: CT: 100~240 seconds; CFT: 30~110 seconds; α: 70°~83°; A10: 44~66 mm; MCT: 50~72 mm. Reference ranges of EXTEM: CT: 38~79 seconds; CFT: 34~159 seconds; α: 63°~83°; A10: 43~65 mm; MCT: 50~72 mm. *CT*, Coagulation time; *CFT*, clot formation time, α, alpha-angle; *A5*, amplitude at 5 minutes, *A10*, amplitude at 10 minutes, *MCT*, maximum clot firmness; *EXTEM*, extrinsic thromboelastometry; *INTEM*, intrinsic thromboelastometry.

intravenous administration of factor concentrates, which is demanding and expensive.

Evidence-based guidelines are lacking for patients with HBD requiring CPB surgery.¹⁻³ Due to the various degrees of factor deficiency, it is impossible to make a general treatment protocol for all patients with HBD. There are no established evidence-based recommendations for optimal levels of FVIII during and after surgery and the optimal duration of replacement treatment. Recently, gene therapy is an advanced therapy offering the potential for a cure or a reduced need for additional coagulation factor–replacement therapy.⁴

Patients with moderate or severe hemophilia A undergoing cardiac surgery usually need a high total dose of FVIII replacement (50,000~94,500 IU of total factor consumption, 714~1260 IU/kg).^{2,5} For our case, the patient received a lower total dose of FVIII replacement (41,000 IU, 506 IU/kg). The blood loss after operation was similar to that of patients without hemophilia.

The perioperative and postoperative protocols were the same, except for the replacement of FVIII concentrate. This was our first case of severe hemophilia A to undergo cardiac surgery after receiving gene therapy. A lower total

dose of FVIII replacement may be anticipated as more experience is gained.

CONCLUSIONS

We performed cardiac surgery safely on a patient with severe hemophilia A who had previously received gene therapy. The blood loss in this patient was comparable with the drain output from our patients without HBDs who received CABG. Close teamwork between surgeon and a comprehensive multidisciplinary hemophilia team is essential to achieve optimal results.

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