Gene therapy and cardiac surgery in a patient with hemophilia

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In hemophilia A, the factor level of FVIII is below 1% of normal. The disease results in various degrees of FVIII deficiency. From the Centers for Cardiovascular Disease and Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan. Disclosures: The authors reported no conflicts of interest.

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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. 1,2 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. 3 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.

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

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 have 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.

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 anti-platelet 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.³ However, the relatively short half-life of FVIII in the circulation requires frequent 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

![FIGURE 1. The series of factor VIII level during hospitalization. POD, Postoperative day.](image1)

![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.](image2)
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). 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.

References