Gene therapy and cardiac surgery in a patient with hemophilia

Running Head: Gene therapy and cardiac surgery in a patient with hemophilia

Authors: Ming-Yuan Kang, MD¹; Jiaan-Der Wang, MD²; Hao-Ji Wei, MD¹

Institution:

¹Center for Cardiovascular Disease, Taichung Veterans General Hospital, Taichung, Taiwan

²Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan

Address: Cardiovascular Center, Taichung Veterans General Hospital, 1650 Taiwan Boulevard, Sec. 4, Taichung 40705, Taiwan, R.O.C.

Keywords: Hemophilia A, gene therapy, cardiac surgery
Corresponding author: Hao-Ji Wei, MD

Address: Cardiovascular Center, Taichung Veterans General Hospital, 1650 Taiwan Boulevard, Sec. 4, Taichung 40705, Taiwan, R.O.C.

Tel.: 886-4-23592525 ext. 5049

Fax: 886-4-23741206

Email address: weihaoji@vghtc.gov.tw

All of the authors declare no conflicts of interest. No funding was received to assist with the preparation of this manuscript.

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CE22221A) at May 19, 2022

The total word count of the manuscript: 809
Central Message

We performed cardiac surgery safely on a patient with severe hemophilia A who had previously received gene therapy. Close teamwork between surgeon and a comprehensive multidisciplinary hemophilia team is essential in order to achieve optimal results.

Central Picture Legend

Figure 1: the results of rotational thromboelastography

CT: Coagulation Time, CFT: Clot Formation Time, α: Alpha-angle, A5: Amplitude at 5 min, A10: Amplitude at 10 min, MCT: Maximum Clot Firmness, s: second. Reference ranges of INTEM: CT: 100~240 s, CFT: 30~110 s, α: 70°~83°, A10: 44~66 mm, MCT: 50~72 mm. Reference ranges of EXTEM: CT: 38~79 s, CFT: 34~159 s, α: 63°~83°, A10: 43~65 mm, MCT: 50~72 mm.
49 **Abbreviation**

50 CABG: coronary artery bypass grafts

51 CAD: coronary artery disease

52 HBDs: hereditary bleeding disorders
Abstract

Objectives: Because the life expectancy of hemophilia patients is now similar to that of the general population, the prevalence of age-related cardiovascular diseases has increased. However, cardiac surgery is extremely challenging for hemophilia patients because of the increased peri-operative bleeding risk. We present our experience with a severe hemophilia A patient who received gene therapy and underwent cardiac surgery.

Methods: A severe hemophilia A patient (the Factor VIII level was < 1% prior to gene therapy) who received AAV5-based gene therapy was diagnosed with CAD-III and underwent coronary artery bypass grafts. The peri-operative data were evaluated retrospectively.

Results: The parameters of ROTEM were in the normal range before operation. The perioperative and post-operative protocols were the same for this patient as for our non-hemophilia patients, except for the replacement of FVIII concentrate. The patient received a lower total dose of FVIII replacement (41,000 IU, 506 IU/kg) during the
perioperative period than is typically required for severe hemophilia A patients. The

blood loss at four hours and eight hours postoperatively was 480 mL and 500 ml,

respectively. This was comparable to the drain output from our patients without a

hereditary bleeding disorder who undergo CABG. The endotracheal tube was

removed on POD 1. The antiplatelet drug, Acetyl salicylic acid 100 mg, was given

since POD 1. The patient was discharged on POD 8 uneventfully.

Conclusions: We performed cardiac surgery safely on a patient with severe

hemophilia A who had previously received gene therapy. Closed teamwork between

surgeon and a comprehensive multidisciplinary hemophilia team is essential in order

to achieve optimal results. A lower total dose of FVIII replacement and reduced

medical expenses may be anticipated as more experience is gained.
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 factor VIII deficiency. In hemophilia A, the factor level of <1% is classified as severe, 1-5% as moderate, and > 5% as mild. With improvements in care, the life expectancy of hemophilia patients has increased. As a consequence, more hemophilia patients are encountering age-related comorbidities, which may need cardiac surgery. However, cardiac surgery is extremely challenging for them because of the increased bleeding risk. Currently, gene therapy is an advanced therapy because it offers the potential for a cure through endogenous production of coagulation factor or a reduced need for additional coagulation factor replacement therapy. We present a patient with severe hemophilia A who had received gene therapy and who subsequently underwent on-pump coronary artery bypass grafts (CABG) safely by correcting the coagulopathy using a lower total dose of Factor VIII 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’s 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 Oct 2019. He was diagnosed to as having coronary artery disease (CAD) with the initial symptoms of dyspnea on exertion. The Coronary angiogram demonstrated 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 (ACT) greater than 400 seconds. During operation, tranexamic acid was given with continuous drip
of 200 mg/hour for 10 hours. The total aortic cross-clamping time was 124 minutes, and the total bypass time was 166 minutes. 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 patient received preoperative preparation. Examination of rotational thromboelastography (ROTEM) was performed before systemic heparization for the CPB. One loading dose of 4000 IU rFVIII (Kovaltry®, 50 IU/kg) 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 (POD) 1 and 2 in order to keep the trough level of FVIII above 80%. A dose of 4000 IU rFVIII (50 IU/kg) was given at POD 3. A dose of 3000 IU rFVIII (37.5 IU/kg) was then given at POD 4 and 5 to maintain a trough level above 60%. The serious level of factor VIII was showed in Figure 2.
The parameters of ROTEM were in the normal range (Fig 1). The estimated blood loss was 900 mL during 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 intra-operatively.

The blood loss at four hours and eight hours postoperatively was 480 mL and 500 mL, respectively. This is comparable to 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 four hours and 571 mL at eight hours.

The endotracheal tube was removed on POD 1. The antiplatelet drug, Acetylsalicylic acid 100 mg, was given since POD 1. He was transferred to an ordinary ward on POD 4, and discharged on POD 8 uneventfully.
Cardiac surgery is an extreme challenge for hemophilia patients. Coagulopathy caused by heparinization, cardiopulmonary bypass, hypothermia, sternotomy, and post-operative thromboprophylaxis raise the intra- and post-operative bleeding risk.\textsuperscript{1,4}

Replacement of the deficient coagulation factor is usually the cornerstone of treatment. The advent of recombinant factor VIII has eliminated the infective risk associated with factor concentrates, such as FFP.\textsuperscript{2} However, the relatively short half-life of factor VIII in the circulation requires frequent IV administration of factor concentrates, which is demanding and expensive.

Evidence-based guidelines are lacking for HBD patients requiring CPB surgery.\textsuperscript{1,4,5} Due to the various degrees of factor deficiency, it is impossible to make a general treatment protocol for all HBD patients. 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.\textsuperscript{2}

Moderate or severe hemophilia A patients 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 non-hemophilia patients.

The perioperative and post-operative 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 to the drain output from our patients without a hereditary bleeding disorders who received CABG. Close teamwork between surgeon and a comprehensive multidisciplinary hemophilia team is essential in order to achieve optimal results.
References


Figure 1: the results of rotational thromboelastography

CT: Coagulation Time, CFT: Clot Formation Time, α: Alpha-angle, A5:
Amplitude at 5 min, A10: Amplitude at 10 min, MCT: Maximum Clot Firmness,
s: second. Reference ranges of INTEM: CT: 100–240 s, CFT: 30–110 s, α: 70°–83°, A10: 44–66 mm, MCT: 50–72 mm. Reference ranges of EXTEM: CT:
38–79 s, CFT: 34–159 s, α: 63°–83°, A10: 43–65 mm, MCT: 50–72 mm.

Figure 2: the serious level of Factor VIII during hospitalization
<table>
<thead>
<tr>
<th></th>
<th>INTEM S</th>
<th>EXTEM S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>167s</td>
<td>55s</td>
</tr>
<tr>
<td>CFT</td>
<td>91s</td>
<td>106s</td>
</tr>
<tr>
<td>α</td>
<td>71°</td>
<td>69°</td>
</tr>
<tr>
<td>A5</td>
<td>45mm</td>
<td>45mm</td>
</tr>
<tr>
<td>A10</td>
<td>57mm</td>
<td>56mm</td>
</tr>
<tr>
<td>MCF</td>
<td>64mm</td>
<td>64mm</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>CFT</td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>INTEM S</strong></td>
<td>167</td>
<td>91</td>
</tr>
<tr>
<td><strong>EXTEM S</strong></td>
<td>55</td>
<td>106</td>
</tr>
</tbody>
</table>