Introduction

Hemophilia A is an X-linked disease caused by deficiency or dysfunction of coagulation factor VIII and its prevalence is approximately 1/10,000. Previously, patients with hemophilia rarely underwent cardiac surgery because of their limited lifespan. However, improved management of hemophilia has led to longer survival, so ischemic heart disease will become more frequent in these patients. Patients with hemophilia are affected by the same cardiovascular risk factors as individuals without hemophilia, and may be more susceptible to certain standard risk factors such as hypertension, obesity, dyslipidemia, and diabetes. Cardiac surgery has a major influence on the hemostatic system. We report a patient with hemophilia A who underwent off-pump coronary artery bypass grafting (CABG) for ischemic heart disease and was successfully managed by continuous infusion of recombinant factor VIII (rFVIII) during the perioperative period.

Case report

The patient was a 55-year-old man with hemophilia A. He had been diagnosed with hemophilia A at the age of 40 years, but had not received treatment because it was mild hemophilia without complications. His cousin and maternal grandfather also had hemophilia A. One month before surgery, the patient noted chest pain that lasted for about 5 minutes. His local doctor suspect vasospastic angina and he was referred to our hospital. The past medical history included hypertension and dyslipidemia. He was taking a beta-blocker, calcium blocker, and aspirin, but was not on a lipid-lowering agent before surgery. On admission, the patient’s height was 168 cm and weight was 68.9 kg. Laboratory tests revealed that Low density lipoprotein-cholesterol was 163 mg/dL. The cross mixing test showed a deficiency pattern, with coagulation factor VIII activity of 12.4%, indicating mild hemophilia A. Factor VIII inhibitor was negative. The electrocardiogram showed a heart rate of 63 bpm with negative T waves in leads II, III, and aVf. On a chest X-ray film, the cardiothoracic ratio was 0.54 and the costophrenic angles were sharp. Transthoracic echocardiography revealed an ejection fraction of 57% with no left ventricular asynergy. Based on these findings, we suspected ischemic heart disease. Cardiac catheterization identified severe triple vessel disease with chronic total occlusion of the left anterior descending artery and severe stenosis of the left circumflex and right coronary arteries (Fig. 1). Percutaneous coronary intervention (PCI) is associated with a lower risk of bleeding compared to CABG. Because this patient had triple-vessel disease, was not so old, and had few risk factors for surgery besides his coagulation disorder, we thought that CABG was better than PCI considering the long-term outcome. Accordingly, we decided to perform off-pump CABG.

Key words: Off-pump coronary artery bypass surgery, hemophilia A, recombinant factor VIII

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At 12 days before surgery, he received a bolus of rFVIII (3000 U) for the factor VIII replacement test. At 3.5 hours after administration, the factor VIII level was 64.3% and the activated partial thromboplastin time (APTT) ratio was 1.25. At 6 days before surgery (the day after cardiac catheterization), the factor VIII level was 59.7% and the APTT ratio was 1.30. From these data, we considered that the 50% factor VIII level corresponded to an APTT ratio of 1.30.

On the day of surgery, he received a bolus of rFVIII (7000 U) before the operation. After surgery commenced, continuous infusion of rFVIII was initiated at a rate of 200 U/h. Off-pump CABG was performed under heparinization without an extracorporeal circuit. Before anastomosis, the activated clotting time (ACT) was 119 seconds, so 11 ml of heparin was administered. The left internal mammary artery was anastomosed to the left anterior descending artery and the right internal mammary artery was anastomosed to the first diagonal artery, while venous grafts were used for the right coronary artery and the left circumflex artery. After completion of anastomosis, 11 ml of protamine was administered, with the ACT being 136 seconds. The factor VIII level was 81.4% at that time, so he received an additional 700 U bolus of rFVIII. Total blood loss during surgery was 480 mL and intraoperative blood transfusion was not performed. Postoperatively, infusion of rFVIII was continued at 300 U/h on the day of surgery. The patient was extubated 5 hours after arrival in the intensive care unit. Up to 24 hours after surgery, the total volume of chest tube drain fluid was 200 ml, followed by a decrease to 100 ml during the next 24 hours, and the drain was removed on the second postoperative day. Infusion of rFVIII was continued until the 10th postoperative day, targeting APTT ratio of 1.3 (Fig. 2). The patient also received additional antiplatelet therapy with 100 mg of aspirin daily. For secondary prevention of ischemic heart disease, he received a beta-blocker, an angiotensin II receptor blocker, and a lipid-lowering agent. Transfusion of packed red blood cells (2 U) was done on the second postoperative day. No bleeding complications occurred. On the 7th postoperative day, coronary artery computed tomography confirmed patency of all bypass grafts (Fig. 3). The subsequent course was uneventful and the patient was discharged on the 13th postoperative day. He continues to do well at one year after surgery.

**Discussion**

In the past, occurrence of coronary artery disease in patients with hemophilia A has been rare because hemophilia is uncommon and patients often died of hemorrhagic
complications at a young age. However, mortality due to hemorrhagic complications has improved owing to the availability of rFVIII and longer survival is leading to an increase of ischemic heart disease in patients with hemophilia. Therefore, it is likely that performing cardiac surgery in hemophilia patients will become more frequent, and control of coagulation during the perioperative period is important for a successful outcome. In the present patient, we performed bolus injection of rFVIII just before commencing the operation, followed by continuous infusion of rFVIII during off-pump CABG after surgery. We considered that off-pump CABG would be effective for preventing intraoperative bleeding complications compared with on-pump CABG. After on-pump CABG, typical problems include excessive bleeding, blood transfusion, and reopening the chest due to bleeding. In contrast, off-pump CABG is associated with normal platelet function and weak activation of the fibrinolytic system.

A review of open heart surgery for adult hemophilia patients assessed 32 patients treated from 1980 to 2013, including 15 patients with isolated CABG (on-pump CABG = 12, off-pump CABG = 3). On-pump CABG was done in 4 patients with severe hemophilia A, 3 with moderate hemophilia A, and 5 with mild hemophilia A, while all 3 off-pump patients had severe hemophilia A. There was one hemorrhagic complication in a patient receiving on-pump CABG, while no hemorrhagic complications were observed after off-pump CABG.

The method of rFVIII administration should be planned by an interdisciplinary team consisting of the cardiac surgeon, anesthesiologist, and hematologist. Several reports have indicated the effectiveness of continuous perioperative infusion of coagulation factor concentrates in patients undergoing cardiac surgery. However, bolus infusion of factor concentrates is also performed, and it is unclear which method is better. The Japanese guideline on replacement therapy for acute bleeding and surgical prophylaxis in hemophilia patients without inhibitors states that continuous infusion of factor concentrates during the operation is advantageous.

High peak levels of factor VIII activity may cause thrombotic complications, whereas low levels may lead to bleeding complications. It is recommended to maintain the factor VIII level above 100% during surgery and above 50% in the early postoperative period. At our hospital, continuous infusion of rFVIII was performed during the postoperative period aiming at an APTT ratio of 1.3, because measurement of factor VIII activity is costly and we predicted that the 50% factor VIII level would be equal to an APTT ratio of 1.30.

We performed postoperative antiplatelet therapy according to the standard clinical guidelines because platelet function is qualitatively and quantitatively normal in hemophilia patients. However, we need to be careful of postoperative bleeding because coagulation is not normal. It has been reported that the extent of coronary atherosclerosis may be comparable between patients with and without hemophilia, so it is important to screen and treat atherosclerotic risk factors in hemophilia patients.

In the present case, the outcome of surgery was successful when we employed continuous infusion of factor VIII concentrate, off-pump CABG, and low-dose antiplatelet therapy with reference to the literature.

Conclusion

We successfully managed a patient with hemophilia A who underwent off-pump CABG. Hemophilia patients with coronary risk factors such as hypertension and dyslipidemia may develop coronary artery disease. Off-pump CABG is useful for preventing bleeding complications.
Disclosure Statement

There is no conflict of interest.

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