Case report - Congenital
Open-heart surgery in an infant with heterozygous factor VII deficiency

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Abstract

A four-month-old male with Taussig–Bing anomaly and multiple ventricular septal defects underwent an open-heart palliative procedure. He suffered from massive postoperative gastrointestinal bleeding. Heterozygous Arg402Stop-related factor VII deficiency was detected by genomic examinations. When he was 14 months old, a subsequent open-heart surgery with replacement therapy of recombinant factor VIIa was performed without any bleeding or thromboembolic complications. Although heterozygous factor VII deficiency is generally recognized as clinically asymptomatic, this latent bleeding disorder can appear perioperatively or postoperatively in patients who undergo cardiopulmonary bypass procedures. Consequently, the prophylactic replacement therapy with recombinant factor VII is recommended during cardiac operations.

Keywords: Pediatric; Congenital heart disease; Genes/polymorphisms; Perioperative care

1. Introduction

Congenital factor VII (FVII) deficiency is a rare bleeding disorder. Severe bleeding episodes are observed in homozygous or compound heterozygous individuals, and hemostasis can be achieved in heterozygous individuals. Although a few reports have addressed open-heart surgery in heterozygous FVII deficient patients [1, 2], there have been no reports concerning open-heart surgery in heterozygous FVII deficient patients. We herein report an infant with heterozygous FVII deficiency who experienced a severe bleeding complication after open-heart surgery. This infant was successfully managed by replacement therapy with a recombinant factor VIIa (rFVIIa; Novoseven, Novo Nordisk, Bagsvaerd, Denmark) during a subsequent surgery.

2. Case report

A male infant with Taussig–Bing anomaly and Swiss cheese-type multiple ventricular septal defects underwent ligature of a patent ductus arteriosus and pulmonary artery banding (PAB) at 14 days of age. Subsequently, a right-sided Blalock–Taussig shunt was performed for progressive cyanosis at two months of age. At four months of age, cardiac catheterization revealed pulmonary hypertension due to a restrictive atrial septal defect. Therefore, enlargement of the atrial septal defect and additional PAB were performed via cardiopulmonary bypass (CPB). Two units of red blood cells were transfused perioperatively, but fresh frozen plasma (FFP) was not administered. From postoperative day 2, he suffered from intractable hematemesis and melena for four days. The laboratory data on postoperative day 2 revealed that the patient’s platelet count was 175 × 10^9/l, prothrombin time (PT) was 56% of normal, international normalized ratio (INR) was 1.47, and activated partial thromboplastin time (APTT) was 43.7 s. Previous coagulation tests showed mild prolongation of PT (52–73%) and INR (1.22–1.73), despite the absence of warfarin administration. His plasma procoagulant activity of FVII was 29% of normal, while all other coagulation factors were within the normal range. Antibodies against FVII were not detected by cross-mixing experiments. After obtaining informed consent, genomic examinations revealed that the patient and his father had heterozygous Arg402Stop mutation (Fig. 1). No other mutations which cause different genotypes (homozygous or compound heterozygous) were detected. At 14 months of age, a bi-directional Glenn shunt with a Damus–Kaye–Stansel procedure and right pulmonary artery plasty under CPB and cardioplegic arrest were scheduled. The preoperative FVII activity was 70% of normal. His parents were informed of the purpose and risk of the use of rFVIIa, and they gave written informed consent. Prophylactic intravenous rFVIIa was administered at a dose of 30 μg/kg. The initial dose was given at the beginning of the operation. The patient was uneventfully weaned from 276 min of CPB. However, hemostasis was difficult due to...
the bleeding tendency despite the antagonization of heparin. The FVII level at that time was 30% and the INR was 1.72. The administration of a second dose of rFVIIa dramatically reduced the bleeding. Postoperatively, the same dose of rFVIIa was administered every 6 h, and the dosing interval was prolonged with the monitoring of INR. In addition, FFP was continuously administered for two days. The rFVIIa therapy was terminated on the fourth postoperative day without any bleeding or thromboembolic complications. During this period, the FVII level was 84–200% and the INR was 0.67–1.16. The patient’s postoperative course was uneventful and he was eventually discharged from the hospital. At 30 months of age, a Fontan procedure was performed using the same replacement protocol without any bleeding or thrombotic complications.

3. Discussion

FVII deficiency is the most common of the rare autosomal recessive inherited bleeding disorders. The condition has an estimated prevalence of one in 400,000. Although patients with heterozygous FVII deficiency are either clinically asymptomatic or present only mild bleeding tendency [3, 4], the current case suffered from severe bleeding after his initial open-heart surgery. The three possible reasons for the postoperative bleeding included increased intraoperative bleeding due to heparinization, augmentation of hemodilution by CPB without FFP transfusion, and impaired FVII synthesis in the liver because of postoperative malnutrition. These factors might have caused a transient decrease in FVII and the consequent bleeding complications.

We performed a second open-heart procedure with the use of the rFVIIa. Intravenous administration of rFVIIa is now widely used for the treatment of FVII deficiency [5, 6]. Recently, the salvage use of rFVIIa for uncontrollable bleeding in cardiac operations has been reported [7, 8]. However, no references were found on the use of replacement therapy for patients with heterozygous FVII deficiency. It is generally accepted that hemostasis can be achieved by raising the FVII activity level above 10–15% of normal [6]. However, FVII activity does not necessarily correlate with the severity of the bleeding tendency. The patient experienced bleeding complications despite the fact that his intraoperative and postoperative FVII coagulation activities were approximately 30%. We confirmed the effectiveness of an additional dose of rFVIIa in the second open-heart operation.

The major concern about the safety of rFVIIa is thromboembolic events (stroke, myocardial infarction, and deep venous thrombosis). Zangrillo et al. recently reported a systematic review and meta-analysis of rFVIIa in cardiac surgery patients, suggesting a non-significant reduction in the rate of surgical re-exploration with a trend toward an increase in the rate of perioperative stroke [9]. The risk of thrombosis in FVII-deficient patients treated with rFVIIa is unknown, especially in heterozygous FVII-deficient patients. Though the current case did not develop thrombosis, the risk of thrombosis should be taken into account in the replacement therapy and excessive administration of rFVIIa should be avoided. Our dose regimen was within the protocol for FVII-deficient patients (15–30 μg/kg every 4–6 h). This dose is considerably less than the dose generally used in patients with hemophilia (90 μg/kg every 2–3 h until hemostasis) or the salvage dose for persistent bleeding in adult cardiac operations (90–100 μg/kg 1–3 doses) [5, 7, 8].

In conclusion, heterozygous FVII deficiency may cause bleeding complications both during and after open-heart surgery. In those cases, perioperative replacement therapy with low dose rFVIIa appears to be efficacious, though optimal dosage and timing are yet undetermined.

References