

## Case Report

### Successful coronary artery bypass graft surgery in severe congenital factor VII deficiency: Perioperative treatment with factor VII concentrate

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**C**ongenital factor VII deficiency is a rare autosomal recessive bleeding disorder with an estimated incidence of 1:500,000 (1). Mild FVII deficiency is associated with an increased risk of posttraumatic and postoperative bleeding, while severe deficiency is associated with easy bruising and spontaneous bleeding, such as mucosal, intraarticular or intracranial hemorrhage (2).

In cardiovascular surgery under cardiopulmonary bypass (CPB) the risk of postoperative bleeding is increased due to systemic anticoagulation, hemodilution, loss of coagulation factors, hyperfibrinolysis and platelet dysfunction. The increased risk of perioperative hemorrhage in patients with pre-existing coagulation disorders can be significantly aggravated when cardiopulmonary bypass is required. In view of the increased morbidity and mortality associated with allogeneic blood transfusions in cardiac surgical patients suffering excessive postoperative bleeding, safe and effective treatment of a pre-existing coagulation disorder is desirable (3).

We report on a patient with severe FVII deficiency who was successfully treated with plasma-derived FVII concentrate for the prevention of bleeding after coronary artery bypass grafting (CABG) using CPB.

#### Case presentation

A 75-year-old Caucasian male, in whom a congenital severe Factor VII deficiency had been diagnosed 12 years before, was scheduled for CABG under CPB for severe 3-vessel cardiac disease. The patient reported episodes of gum-bleeding and mild epistaxis up to the age of 24 and postoperative bleeding after cholecystectomy. FVII activity prior to surgery was below 2%

(normal values in author's lab: 60–130%). Acetylsalicylic acid had been discontinued for seven days.

Prior to cardiopulmonary bypass 1.5 Mio KIU aprotinin (Trasylol<sup>®</sup>, Bayer Vital GmbH, Leverkusen, Germany) and 350 IU/kg heparin (Liquemin<sup>®</sup>, Hoffmann-La-Roche, Grenzach-Wyhlen, Switzerland) were given followed by one additional bolus of heparin (50 IU/kg) during CPB to maintain an activated clotting time (ACT) of at least 480 s. Priming of the extracorporeal circuit included HES 10%, balanced electrolyte solution, heparin (8000 IU) and aprotinin (3 Mio KIU). Warm intermittent blood cardioplegia was used.

Plasma-derived FVII concentrate (Faktor VII S-TIM 4 IMMUNO 600 I.E.<sup>®</sup>, Baxter Deutschland GmbH, Unterschleißheim, Germany) was used for prevention of postoperative bleeding. Substitution started immediately after the end of cardiopulmonary bypass (CPB) with an initial bolus of 20 U FVII / kg (1,800 U) followed by a fixed dose of 7 U FVII / kg (600 U) at 4, 10, 16, 24, 32 and 40 hours (Fig. 1). On postoperative day 2 the dosage interval was extended to 12 hours until postoperative day 7. FVII level and PT seconds were determined before and after each substitution for the first 96 postoperative hours (until day 4 post surgery) and are shown in Figure 1.

The surgical procedure was uneventful and consisted of sequential saphenous vein grafts to marginal artery (M1) and ramus intermedius (RIM) and left internal mammarian artery (LIMA) to left anterior descending artery (LAD). During CPB 4 units of packed red cells (PRC) were transfused due to the low hematocrit (0.31) prior to surgery to prevent a critical decrease in oxygen delivery, which has the potential to impair organ function (4). After weaning from CPB the patient developed ST segment elevation and ventricular fibrillation despite patent grafts. This was successfully treated with defibrillation, 100 mg lidocaine, and 2 mg magnesium. After reversal of heparin (ACT 120 sec) the chest was closed and the patient was transferred to ICU without any signs of bleeding. Coagulation parameters and records of drainage loss are given in Figure 1. There was no significant postoperative bleeding (Fig. 1) and replacement therapy was carried out as scheduled. Continuous intravenous low-dose heparin (250 IU/h) and acetylsalicylic acid 100 mg/d were started 6 h postoperatively. On postoperative day 4 the patient was discharged to an intermediate care unit in a stable condition. FVII replacement was continued until day 7. The postoperative course was uneventful and no further blood products were required.

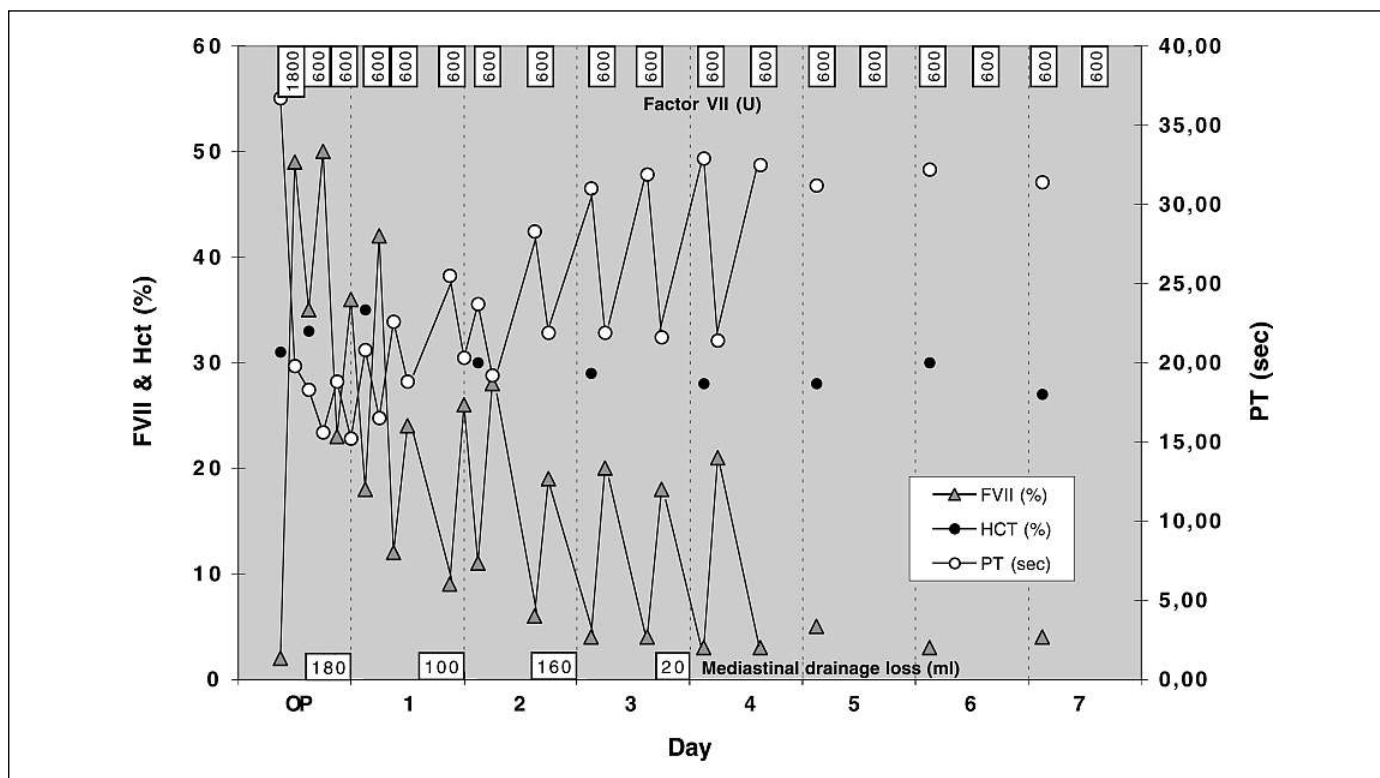
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**Figure 1: Factor VII levels, PT seconds and drainage loss during perioperative replacement therapy with plasma-derived FVII (Faktor VII S-TIM 4 IMMUNO 600 I.E.<sup>®</sup>). Mediastinal drainage loss did not increase with prolonged substitution interval. The drainage was removed on the 3<sup>rd</sup> postoperative day. Normal values in author's lab: FVII: 60–130%; PT (sec): 12.9–14.5 sec.**

## Discussion

We report on the successful preventive use of plasma-derived FVII concentrate in a patient with severe factor VII deficiency undergoing CABG surgery.

For congenital FVII deficiency it is difficult to define a FVII activity threshold value at which prophylactic replacement therapy is indicated (2). Perioperative replacement therapy may not be necessary for minor surgical procedures in patients with severe FVII deficiency provided that there is no history of severe haemorrhagic episodes (5, 6). It seems that bleeding is unlikely to occur as long as FVII levels are above 10–15% of normal (7, 8). With a FVII level of <2% and a history of postoperative bleeding, our patient was at high risk for severe bleeding during and after CABG surgery (5, 9). In the case of life-threatening bleeding, FVII levels should be maintained above 20% (10).

Plasma-derived FVII concentrate and recombinant activated Factor VII (rFVIIa, NovoSeven<sup>®</sup>) are approved replacement therapies in FVII deficiency (2, 14–20). To our knowledge there have been four previous case reports of cardiac surgery in patients with congenital FVII deficiency (11–13, 15) and one of cardiac surgery on an infant with FVII deficiency of unknown origin (14). Additionally, the uses of prothrombin complex concentrate and fresh frozen plasma (11) have been reported in such cases.

The FVII concentrate we used in our patient was pooled human plasma derived FVII concentrate “Faktor VII S-TIM 4 IMMUNO 600 I.E.<sup>®</sup>”, manufactured by Baxter Deutschland GmbH, Unterschleißheim, Germany. According to the manufacturer the intrinsic activity of the product is  $\geq 2$ U factor VII / mg

protein. The reconstituted product contains < 0.2 U FII/U FVII, < 0.15 U FIX/U FVII and < 0.35 U FX/U FVII. Our goal was an average factor VII level of > 20–30% during the first 48 h after surgery and peak levels for factor VII of approximately 20% for the following days. For this purpose we used a regimen with an initial bolus von 20 U/kg, followed by a fixed dose of 600 U FVII (7 U/kg) and increasing dosage intervals. Following this dosing regimen neither excessive drainage loss nor transfusion of blood products occurred after surgery. Increases in FVII activity were well predictable in the perioperative setting with a mean increase of  $2.38 \pm 0.49\%$  (Mean  $\pm$  SD) per Unit FVII / kg body weight. Mean factor VII level during the first two days after surgery was 28% (min-max: 9 – 50%). As a result of extending the dosing interval to 12 hours on the second postoperative day average FVII activity fell to 12% (min-max: 3 – 21%). At this point in the postoperative course, when clots in the surgical field have been formed, it may be safe to allow the FVII activity to fall.

Our reason for using plasma-derived FVII was to establish an algorithm, which uses the replacement of the missing clotting factor as the first line treatment. Recombinant FVIIa as a pharmacological approach (21) remained as a further treatment option in case refractory bleeding would develop despite FVII replacement (14).

We conclude that plasma-derived FVII at the given dosage is a safe, effective and predictable replacement therapy in FVII deficiency in cardiac surgery patients. Recombinant FVIIa remains a therapeutic option when plasma derived FVII fails to control bleeding.

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