Use of Thromboelastograph and Factor VII for the Treatment of Postoperative Bleeding in a Pediatric Patient on ECMO After Cardiac Surgery

Matthew C. Davis, ECCP,* Niels E.O. Andersen, MD;† Per Johansson, MD;‡ Lars W. Andersen, MDSc, MD†

*Department of Cardiothoracic Surgery, †Department of Cardiac Anaesthesia, and ‡Department of Haematology, Rigshospitalet, Copenhagen, Denmark

Abstract: This report describes a case of possibly fatal bleeding treated successfully with an “overdose” of recombinant factor VII (rFVII; Novo7). A 3.5-year-old boy had surgery for aortic stenosis and aortic arch repair and was placed on extracorporeal membrane oxygenation (ECMO) after a prolonged cardiopulmonary bypass time (CPB); there was subsequent failure to wean from CPB because of right ventricular failure. Subsequently, a severe coagulopathy developed, and despite large volume transfusions with blood and blood products, this was unresolved. Thromboelastograph (TEG) measurements were obtained, and on the advice of the Hematology Department, Novo7 (recommended dose: 15–30 μg/kg) was administered at a dose of 200 μg/kg because of the severity of the bleeding. TEG was repeated, and a further dose of Novo7 was administered at 500 μg/kg; a further TEG after 15 minutes showed normalization, and the remaining bleeding was treated surgically. The patient was weaned from ECMO 48 hours later and was subsequently discharged home with no further problems. Novo7 in an “overdose” can apparently correct major coagulopathy even in patients on ECMO support with no dire effects on the ECMO circuit or the patient in a life-threatening scenario. Keywords: thromboelastograph, Factor VII, extracorporeal membrane oxygenation (ECMO), cardiac surgery.

CASE REPORT

A 3.5-year-old, 16-kg boy with a severe supravalvular aortic stenosis (gradient at time of pre-operative echocardiography was 118 mm Hg) underwent open heart surgery, and a supravalvular resection and aortic reconstruction was performed, with a bypass time (BPT) of 251 minutes and an aortic clamp time (XCT) of 121 minutes. Aprotinin at a dose of 120,000 KIU/h was started at the time of anesthetic induction. Just after termination of cardiopulmonary bypass (CPB), the patient developed severe right ventricular failure, and a stenosis of the distal part of the ascending aorta was suspected. CPB was re instituted, and cooling to 19°C was initiated. An extension of the ascending aorta and proximal arcus with a pericardial patch was performed, BPT 121 minutes and XCT 92 minutes. After rewarming, weaning from the perfusion was impossible because of biventricular failure. Extracorporeal membrane oxygenation (ECMO) was instituted under systemic heparinization with a target activated clotting time (ACT) of 150 seconds. The circuit was comprised of our unit’s standard Carmeda-coated pediatric ventricular assist circuit, which includes: 0.25-in internal diameter (ID) tubing throughout, a Biomedicus BP 50 pediatric pump head, and a flow probe. A model 540 Biomedicus console was used for blood propulsion (Medtronic Cardiac Surgery, Kerkrade, Holland), and in addition, a Hilite 2400 LT oxygenator (Medos Medizintechnik AG, Stolberg, Germany); this a non-porous polymethylpentene fiber oxygenator approved for ECMO use in Europe; the original 12F aortic cannula was retained, and a single 22F right atrial cannula was used. Priming was done using 200 mL of plasmalyte solution. Flow was maintained at 1.5 L/min. Auto-transfusion was not used because this is not our routine practice in pediatric patients, and cell saving was not an option because all our units were in use elsewhere. The ACT was 189 seconds at initiation of ECMO. Initial blood results showed an activated partial thromboplastin time (APTT) of 42 (reference range, 23–35) and a P-antithrombin of 0.72 kIU/L (reference range, 0.83–1.15); all other results were unremarkable. Uncontrolled bleeding at 400 mL/h developed in the intensive care unit (ICU), including oozing from venipuncture sites and not
responding to fresh frozen plasma and platelet transfusions. Thromboelastograph (TEG) tracings were severely compromised (Figure 1A and B), and laboratory results at this time were as follows: APTT, 202; hemoglobin (Hb), 5.4 mmol/L (reference range, 6.6–8.1 mmol/L); platelet count, 55 kIU/L (reference range, 150–400); P-antithrombin, 0.55; recombinant factor VII (rFVIIa, NovoSeven; Novo Nordisk A/S, Bagsvaed, Denmark), 200 µg/kg body weight. Fibrinogen (400 mg) was administered without any hemostatic effect. TEG showed a normal coagulation profile in the sample 15 minutes after administration of the rFVIIa infusion, where heparin was neutralized, whereas the native sample continued to be severely compromised (Figure 2A and B). As salvage therapy, rFVIIa at 500 µg/kg body weight was administered, and the TEG pattern 15 minutes after infusion showed an improved coagulation profile in both samples (Figure 3A and B). Bleeding decreased from 400 to 200 mL/h, and the normal TEG pattern indicated that the main cause of bleeding was surgical. Laboratory results at this time were as follows: APTT, 36; Hb, 6.8; platelet count, 63; P-antithrombin, 0.76 kIU/L. Consequently, the chest was reopened, fresh clots along the suture lines were found, and two active sites of surgical bleeding were identified at the distal part of the right internal mammary artery (RIMA) near the pacing electrode and at the site of aortic cannulation. During this period of bleeding, a total of 28 units of SAG-M (packed red cells), averaging 300 mL/unit, 7 units of platelets, and 19 units of fresh frozen plasma (FFP), were administered. Surgical hemostasis was obtained, the bleeding rate decreased successively over the next 12 hours, and the patient was successfully weaned from ECMO 48 hours later. The total transfusion requirements were 38 units of SAG-M, 10 units of platelets, and 31 units of FFP. Laboratory results on discharge from the ICU were as follows: APTT, 30; Hb, 7.1; platelet count, 249; P-antithrombin, 0.99 kIU/L. The child was discharged from the hospital with no obvious neurological sequela.

**DISCUSSION**

Excessive post-operative bleeding after open heart surgery is not uncommon and is associated with severe coagulopathy (1), which is further augmented by a systemic inflammatory response triggered by the CPB procedure (2).

This case was further complicated by systemic heparinization of the patient, making standard coagulation analysis futile. TEG measures the physical properties of the clot and has proven valuable in reducing transfusion requirements in liver transplantation and open heart surgery (3). By analyzing the patients’ blood with and without neutralizing heparin, TEG allowed us to discriminate between the effect of systemic heparinization and coagulopathy secondary to dilution and consumption of coagulation factors and platelets as the cause of bleeding.
rFVIIa has the same structure and functionality as native FVIIa and acts by binding to tissue factor at the site of vascular damage, initiating a local thrombin generation necessary for normal hemostasis. In pharmacological doses, rFVIIa acts directly on the activated platelets by-passing the intrinsic coagulation pathway and has proven valuable in both hemophilic and non-hemophilic patients with massive bleeding (4). Addition of rFVIIa at a dose of 200 µg/kg body weight improved both coagulation ability and clot strength when the heparin effect was neutralized as evaluated by TEG; however, no effect on clinical bleed-
ing was observed. As salvage therapy, a second dose of rFVIIa at 500 µg/kg body weight improved the TEG curve both in the native and the heparin-neutralized sample in concert with the clinical finding. The normal TEG tracing in the native sample together with continued bleeding indicated a surgical cause, and re-exploration was performed, finding fresh clots along the suture lines and two sites of surgical bleeding in concert with the normal coagulation profile. The successful pro-hemostatic effect of rFVIIa corroborates the findings by Verrijckt et al. (5) regarding the beneficial role of rFVIIa in patients with uncontrolled bleeding during ECMO. The substantially higher dose needed for clinical effect in our patient (500 vs. 15–30 µg/kg recommended dose range) could be attributed to a more pronounced bleeding evident by a 50% loss of the total blood volume per hour in our patient, and furthermore, a difference in ACT levels could also affect the dose required. The age of our patient also may have been a contributory factor.

This case shows the value of rFVIIa in a complex cardiac patient with a life-threatening bleeding condition on systemic heparin treatment secondary to ECMO and also underscores the value of TEG in assessment of coagulopathy in complex cardiac patients.

REFERENCES