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# Management of a Patient with Type IIC von Willebrand's Disease during Coronary Artery Bypass Graft Surgery

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VON WILLEBRAND'S disease is the most commonly inherited bleeding disorder with a prevalence as great as 1% of the population.[1] The von Willebrand factor, synthesized by vascular endothelium and megakaryocytes, plays an integral role in platelet adhesion and stabilization of factor VIII.[2] The bleeding associated with von Willebrand's disease (VWD) most often manifests as a defect of primary hemostasis. Therapeutic management of type II VWD during the perioperative period has traditionally consisted of cryoprecipitate administration in an attempt to replace the von Willebrand factor. The risk of viral transmission makes this a less than ideal therapeutic option.** Humate-P (Armour Pharmaceutical, Kankakee, IL) is a third-generation pasteurized factor VIII concentrate derived from human plasma that has recently become available for use in the United States. We describe the first administration of Humate-P for the control of perioperative hemorrhage in a previously untransfused patient with type IIC VWD undergoing coronary artery bypass graft surgery.

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## Case Report

A 51-year-old man with a history of VWD was admitted following an acute inferior myocardial infarction. Cardiac catheterization revealed three-vessel disease with a 99% occlusion of the right coronary artery. Bleeding from the cardiac catheter introducer site was controlled with a pressure bandage.

Preoperative laboratory evaluation was significant for increased activated partial thromboplastin time (aPTT) to 35 s (normal 21–32 s) with a prothrombin time (PT) of 10.4 s (normal 9.2–10.9 s). The bleeding time exceeded 15 min (normal 3–10 min). Factor VIIIC concentration was determined to be 26% of control with ristocetin cofactor < 25% of control and undetectable von Willebrand factor (vWF) antigen. Platelet aggregation failed to occur at 1.5 mg/ml ristocetin. The plasma vWF multimer pattern on SDS-agarose gel electrophoresis was consistent with type IIC VWD (fig. 1); however, the von Willebrand multimer pattern from platelet lysate appeared normal. Preoperative hematocrit was 37% with blood type O-positive.

Anesthesia for cardiac surgery consisted of fentanyl and midazolam infusions with vecuronium for muscle relaxation. Heparin (300 units/kg) was administered for anticoagulation. Cardiopulmonary bypass (CPB) was performed using a membrane oxygenator. The circuit was primed with lactated Ringer's solution, 20% mannitol (200 ml), hydroxyethyl starch (500 ml), and 5,000 units of heparin. A five-vessel bypass was performed using four saphenous vein grafts and the left internal mammary artery. Separation from CPB was uneventful. The activated clotting time was in excess of 600 s throughout CPB. Reversal of anticoagulation with 200 mg protamine returned the activated clotting time to a baseline value of 134 s. Humate-P (2,000 IU iv) was infused over a 15-min period following administration of the protamine. No hemodynamic sequelae were noted. Drainage from the chest tubes decreased to 80 ml by the second hour following surgery. Total chest tube drainage for the first 24 h after surgery amounted to 910 ml. No vasoactive medications were required postoperatively. Plasma samples obtained during the perioperative period were analyzed by SDS-agarose gel electrophoresis and immunoblotting with anti-vWF antibodies (fig. 1). Preoperatively, the patient's plasma vWF multimer pattern (fig. 1, lane C) consisted of a single repeating band that did not form high molecular weight multimers, a pattern consistent with type IIC VWD; however, the vWF differed from a typical type IIC pattern (fig. 1, lane J) in that vWF antigenicity was reduced. Following the intraoperative infusion of Humate-P, the multimer pattern was normal with increased concentrations of high molecular weight multimers (fig. 1, lane G). In addition, the bleeding time decreased to 10 min. Humate-P was continued for 6 days postoperatively. Because of limited supplies of Humate-P, the dosage varied between 1,000–2,000 IU/day (table 1). No blood products other than Humate-P were required during the hospitalization, and

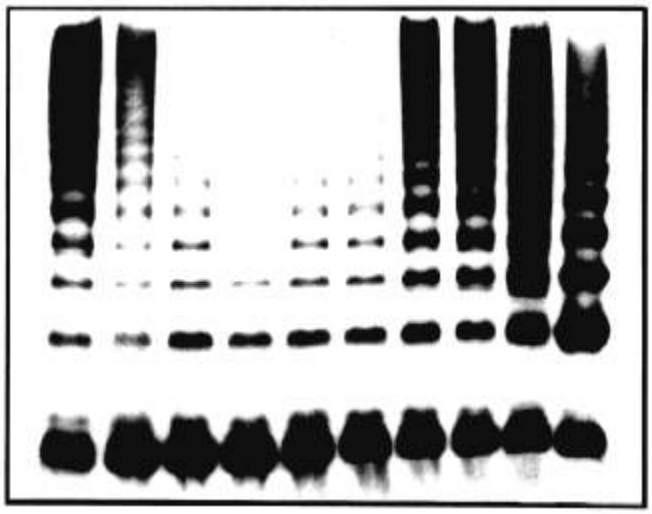


**Fig. 1. SDS-agarose gel electrophoresis with immunoblotting for vWF antigen performed on perioperative patient plasma samples: (*A*) normal plasma control, (*B*) normal platelet control, (*C*) preoperative, (*D*) 15 min after heparin, (*E*) 15 min on cardiopulmonary bypass (CPB), (*F*) 120 min on CPB, (*G*) 15 min after Humate-P, (*H*) 60 min after Humate-P, (*I*) 18 h postoperative following morning dose of Humate-P, and (*J*) type IIC von Willebrand's disease plasma control.**

the patient was discharged 7 days after surgery with a hematocrit of 31%.

## Discussion

Von Willebrand's disease may be divided into a number of subtypes based upon quantitative and qualitative defects in the vWF protein.[2] Determination of the subtype of VWD has proved important for selection of therapy. Type I VWD, a quantitative defect of the vWF multimer, frequently responds to desmopressin acetate.[3] In contrast, administration of desmopressin acetate in type IIB VWD results in platelet aggregation and thrombocytopenia.[4] Subtype classification of VWD relies upon examination of the multimer pattern on SDS-agarose gel electrophoresis.[5] Electrophoresis of the type IIC variant, initially described by Ruggeri *et al.*, has been characterized by: (1) replacement of the normal multimer "triplet pattern" with a repeating unit of predominantly one band, (2) decreased mobility of the major bands as compared to normal plasma, and (3) accentuation of the smallest multimer.[6] Based upon subsequent reports, the IIC variant clearly consists of a heterogeneous group of subtypes recognizable by characteristic multimer patterns on SDS-agarose gel electrophoresis.[7–9]

Humate-P is a pasteurized factor VIII concentrate recently introduced into the United States for the treatment of factor VIII deficiency. In contrast to previous factor VIII concentrates, Humate-P retains considerable von Willebrand factor activity through the manufacturing process. In a comparison with other factor VIII concentrates currently available, Humate-P retained the highest concentrations of vWF antigen and ristocetin cofactor activity.[10] In addition, the large molecular weight multimers that are essential to platelet adhesion are preserved in Humate-P. Pasteurization of factor VIII concentrates has proved highly effective at eliminating viral contaminants.[11] Humate-P has been reported to control hemorrhage unresponsive to desmopressin acetate or cryoprecipitate in patients with VWD.[12,13] Only one prior report exists describing the administration of Humate-P in type IIC VWD. In that non-surgical patient, laboratory parameters became normal following the infusion.[3]

In normal patients the plasma concentration of vWF increases during CPB and into the postoperative period.[14] Rather than replacing the vWF preoperatively, we chose to administer Humate-P following completion of surgical revascularization, thereby decreasing the theoretical risk of thrombotic complications. Our patient's laboratory abnormalities corrected following the administration of Humate-P. SDS-agarose gel electrophoresis of plasma samples after Humate-P demonstrated replacement of the high molecular weight multimers with a return of the normal "triplet pattern" (fig. 1). A single daily dose of 20–25 IU/kg Humate-P increased both factor VIIIC and ristocetin cofactor

**Table 1. Response to Humate-P Infusion in a Patient with Type IIC von Willebrand's Disease**

| | Days after CABG Surgery | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | −1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Humate-P (units) | — | 2000 | 2000 | 2000 | 1000 | 2000 | 1050 | 2000 |
| Factor VIII:C (%) | 26 | 162 | 224 | 384 | 313 | 205 | 245 | 154 |
| R CoF (%) | <25 | 95 | 117 | >120 | >120 | 59 | 88 | 64 |

CABG = coronary artery bypass graft; R CoF = Ristocetin cofactor.

concentrations above the normal range for 24 h (table 1). In the management of hemophilia A following surgery, the package insert for Humate-P recommends doses of 15 units/kg every 8 h for at least 10 days postoperatively. Based upon the severity of both vWF and factor VIIIC deficiencies in our patient, we continued Humate-P infusions for 6 days until the evening prior to discharge.

Several unique features of this patient's disease suggest that he may represent a previously undescribed variant of type IIC VWD. Although the SDS-agarose gel electrophoresis pattern is clearly that of a type IIC defect, the virtual absence of both von Willebrand factor antigen and ristocetin cofactor (ristocetin induces agglutination of platelets in the presence of von Willebrand factor) are consistent with the more severe type III VWD. Type IIC VWD typically does not result in severe decreases in factor VIIIC. Only one prior report of type IIC VWD describes a disparity between the platelet and plasma von Willebrand factor multimer pattern as seen in our patient.[9] The presence of normal platelet von Willebrand factor may account for the relatively minor bleeding history of this patient despite the near absence of von Willebrand factor activity in plasma.[15]

Furthermore, this also may explain the development of coronary atherosclerosis and thrombosis in this patient with a severe deficiency of vWF. Prior investigations have suggested that a deficiency of vWF may protect against coronary artery atherosclerosis and thrombosis.[16,17] It is possible that platelet vWF plays the more important role in these events.

We have described the successful administration of Humate-P for the prevention of bleeding in a patient with VWD undergoing coronary artery bypass graft surgery following an acute myocardial infarction. This factor VIII concentrate recently introduced in the United States offers an effective replacement for von Willebrand factor with a low risk for viral transmission.

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