Factor IX Induced Hypercoagulable State

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Excessive bleeding following cardiopulmonary bypass (CPB) may occur in as many as 5–15% of patients.\(^1\) Various causes include impairment of platelet function,\(^2\) thrombocytopenia,\(^3\) intrahepatic platelet sequestration,\(^4\) dilution of clotting factors with pump prime,\(^5\) inadequate reversal of anticoagulant therapy, disseminated intravascular coagulation (DIC),\(^2\) and hyperfibrinolysis.\(^1,5,6,8\)

Suggested therapy includes infusion of various components of the clotting mechanism, including platelets, fresh frozen plasma, cryoprecipitate and/or prothrombin complex concentrates. However, these blood products may lead to unanticipated and even disastrous consequences. Hypercoagulability and thrombosis,\(^5,9\) including myocardial infarction,\(^10-15\) are complications associated with the infusion of prothrombin complex concentrate in treating patients with hemophilia B. We recently observed acute hypercoagulability with consequent widespread and massive thrombosis in a patient who had received prothrombin complex following cardiopulmonary bypass and insertion of a prosthetic aortic valve with a composite graft.

REPORT OF A CASE

A 63-year-old, 63-kg woman was scheduled for replacement of an aortic valve prosthesis that had been inserted 9 months earlier. At that time a permanent pacemaker also was inserted. The patient did well until 1 month prior to admission, when symptoms of congestive heart failure developed. A diagnosis of prosthetic valve dehiscence and false aneurysm of the sinus valsalva with compression of the left main coronary artery was made. Medical history included controlled hypertension and a mastectomy many years earlier. Preoperative medications consisted of digoxin, nifedipine, isosorbide dinitrate, furosemide, clonidine, and nitroglycerin ointment. Activated clotting time (ACT) measured manually was 110 s, prothrombin time 11.5 s (control 11.4 s), partial thromboplastin time 24.4 s (control 24.6 s), and platelet count 138,000/mm\(^3\). General anesthesia was induced with fentanyl 75 \(\mu g\)/kg and diazepam 20 mg iv, and the patient had a stable course before and during cardiopulmonary bypass. Anticoagulation was effected with a total heparin dose of 27,000 units, and the ACT was increased to 400 s. The prosthetic valve and ascending aorta were replaced with a Shiley Aortic Composite graft \#25. Cardiopulmonary bypass time was 150 min. After adequate rewarming, the patient was weaned from bypass easily, without the need for any positive inotropic drugs. Procainamide 550 mg was administered iv over 15 min to reverse the heparin and the ACT returned to 120 s (control 110 s). Whole blood was not administered in the bypass period or afterward, nor was an autotransfusion system used. Because of persistent oozing, fresh frozen plasma (FFP), 4 units, and platelet concentrate,\(^2\) 10 units, were administered without any changes in hemodynamics. Factor IX concentrate (Proplex\(^\text{®}\)) was infused empirically over 1 h after the FFP and platelets because of persistent oozing and no apparent surgical cause. Fifteen minutes after starting the Factor IX infusion, at which point approximately 700 units had been administered, sudden left ventricular failure developed. This was evidenced by a decrease in arterial blood pressure from 110/60 to 50/20 mmHg; left atrial pressure rose from 17 to 35 mmHg. Shortly before this acute deterioration, the patient's cardiac output was 4.0 L/min and the systemic vascular resistance was not calculated.

When this catastrophic event occurred, it was clear cardiac output was very low. Because the anesthesiology team was fully occupied in preparing and administering drugs, CPB was reinstituted in less than 5–8 min and a repeat cardiac output was not obtained. Body temperature at the time of cardiovascular collapse was 36.6°C. Ionized calcium was not measured, but 2 g calcium chloride were administered iv in divided doses after the administration of fresh frozen plasma and platelets. Procainamide titration was not performed. Cardiac rhythm continued to be a paced rhythm with runs of ventricular tachycardia, and a marked metabolic acidosis developed. Because of this collapse, which was unresponsive to calcium chloride, sodium bicarbonate, ephedrine, and epinephrine drip iv, CPB was reinstituted and the aortic root reexposed. There were large blood clots on the prosthetic valve and the inside (but not the outside) of the graft extending distally past the aortic arch, without any other evidence of valve malfunction. Presumably the clots were throughout the arterial system, since no femoral or radial pulses could be palpated even when there was pulsatile flow. At time of cardiovascular collapse, the chest had been closed. Cardiac tamponade was unlikely, since the pericardium was not closed, and there were two functioning chest tubes in place around the heart. After resuscitation patient was brought to the intensive care unit on epinephrine infusion and left heart bypass. She died later that night. Postmortem examination was not performed.

DISCUSSION

Previous reports of thrombosis following infusion of prothrombin complex concentrate have usually involved areas of low flow and pressure. Thrombotic complications that have been described include superficial vein thrombosis and pulmonary embolism,\(^9,14\) myocardial infarction in a patient with preexisting atherosclerotic heart disease,\(^10\) in three otherwise healthy teenage hemophiliacs.
with no prior evidence of heart disease,11-15 and thrombosis of the portal vein after porta caval shunting.6 So great is the risk of thrombosis in patients receiving Factor IX concentrates that Kasper advocates complete prohibition of elective surgery in patients with hemophilia B.9 Conversely, she also points out that Factor VIII complex, when used to prepare patients with hemophilia A, apparently does not induce a hypercoagulable state. Our case is the first described report of intraoperative thrombosis after administration of Factor IX. Especially alarming is the development of clots in such a high-flow–high-pressure area, as in the ascending aorta. This was a sudden event, as demonstrated by the rapid deterioration from a normal arterial blood pressure, a normal configuration of the arterial pressure curve and pulmonary capillary wedge pressure, to a state of near zero flow. The temporal correlation between clotting and administration of Factor IX complex is striking, as is the absence of any other exogenous substance capable of inducing hypercoagulability.

The normal clotting system consists of primary and secondary hemostatic mechanisms consisting of activation of platelet aggregation, followed by activation of the plasma clotting cascade. Both systems have intrinsic parallel antagonist systems, and maintenance of fluidity and flow is a function of balanced opposition. Plasma clotting factors normally circulate as inactive proenzymes. In the face of a suitable stimulus, partial proteolysis occurs, with conversion of the proenzymes to active forms and recruitment of all components of the clotting cascade to produce thrombosis. The triggering mechanism is ordinarily contact with an endogenous “foreign” substance, such as the collagen endothelial basement membrane, exposed by a tear in a blood vessel. Other “nonphysiologic” stimuli, including Factor IX complexes may cause clot formation at inappropriate times in inappropriate areas.

Disseminated intravascular coagulation (DIC) is manifested initially as increased coagulation and might be triggered by inadequate anticoagulation during cardiopulmonary bypass. However, in our case the ACT of greater than 400 s throughout CPB is evidence of adequate anticoagulation. Furthermore, the hypercoagulable phase of DIC is followed by hypocoagulability for which there was no evidence in our patient. Acute thrombosis was not followed by excessive bleeding from venipuncture or arterial puncture sites, nor in the operative wound.

An alternate explanation for massive thrombosis is low flow secondary to left ventricular failure, as might be associated with drug or fluid administration, manipulation of the heart, acute myocardial infarct, or valve failure. Clotting of the entire aorta would be unlikely, however, even with marked reduction in cardiac output and resultant low flow. The rapid development of extensive clotting evidences a major acute derangement in the clotting mechanism per se and the only identifiable cause is the administration of Factor IX complex.

In vitro and in vivo studies have demonstrated the presence of activated proenzymes in Factor IX concentrates.11,14,15 These thrombogenic enzymes have the potential to trigger the cascade mechanism, resulting in accelerated and extensive clot formation. Attempts to remove activated clotting factors from Factor IX concentrate in order to reduce the risk of spontaneous thrombosis have been unsuccessful.11 Prophylactic anticoagulation in patients needing Factor IX also has been considered.7 Unfortunately, the risk of thrombosis after administration of Factor IX complexes has not been appreciated, and the possibility of sudden, massive clotting must be considered when infusing Factor IX complex for preoperative preparation and perioperative bleeding in surgical patients. The only clear cut indication for the administration of a component of the clotting system is a demonstrated deficiency of that component.

REFERENCES