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RECOMBINANT HIRUDIN FOR EXTENDED AORTIC SURGERY IN PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA

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Anticoagulation with unfractionated heparin is used for complex operations on the thoracic aorta both as a standard regimen for vascular procedure and as an anticoagulant for partial femorofemoral cardiopulmonary bypass. With repeated exposure to unfractionated heparin, heparin-induced thrombocytopenia, a severe antibody-mediated drug reaction, may develop in some patients who have previously received heparin. Most patients have only isolated thrombocytopenia, a complication that usually does not cause major morbidity. Paradoxically, a subset of patients with thrombocytopenia will have thrombotic or thromboembolic complications, possibly because of in vivo platelet activation. The heparin-to-heparin body complexes stimulate platelets with subsequent platelet aggregation, disseminated thrombosis, and embolism with platelet-rich, fibrinolysis-resistant clots.[1] Most episodes of heparin-induced thrombocytopenia are caused by an immunoglobulin G antibody that forms after several days of exposure to heparin. The immunoglobulin G interacts with heparin and the platelet surface to cause activation of platelets. Platelet factor 4 is a necessary cofactor in this disease. It combines with heparin to form a complex to which the heparin-induced platelets bind to platelet factor 4 when platelet factor 4 is complexed with heparin but does not bind to heparin alone.[2] If heparin-induced thrombocytopenia is detected before the operation, anticoagulation with heparin for vascular surgery or cardiopulmonary bypass is precluded and an alternative anticoagulant should be used.[3]

In this report we describe the cases of 2 patients with heparin-induced thrombocytopenia after multiple previous cardiac procedures who successfully underwent extended operations on the aortic arch and descending thoracic aorta. Anticoagulation for cardiopulmonary bypass was performed with recombinant hirudin, a direct thrombin inhibitor.

Clinical summaries. The first patient, a 64-year-old man with depressed left ventricular function (left ventricular ejection fraction of 0.30) and a history of composite graft replacement of the ascending aorta 8 years previously because of acute aortic dissection, was admitted to our institution because of symptomatic aneurysm of the distal part of the aortic arch and the entire descending thoracic aorta with a maximal diameter of 70 mm. After cardiac catheterization, a thrombocytopenia with a platelet count of 60,000 cells/mm^3 developed. The diagnosis of heparin-induced thrombocytopenia type II was confirmed by heparin-induced thrombocyte activation assay. The patient underwent replacement of the distal part of the aortic arch and descending thoracic aorta with partial femorofemoral cardiopulmonary bypass and hirudin as anticoagulant. The postoperative amount of drained blood was 850 mL. In total he received 4 units of erythrocyte concentrates and 6 units of fresh-frozen plasma. The postoperative course was completely uneventful.

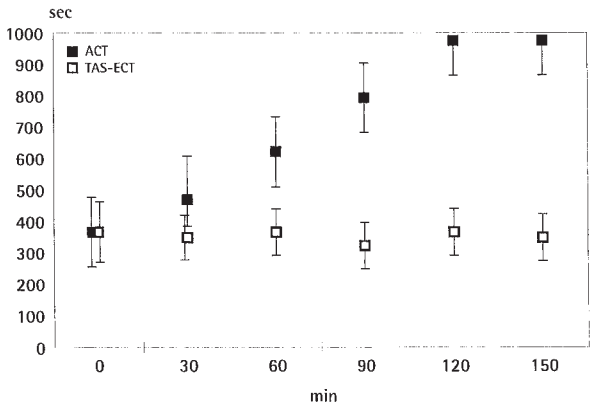

Fig 1. Recombinant hirudin concentration online-measured by ecarin clotting time *(TAS-ECT)* and activated clotting time *(ACT)* during cardiopulmonary bypass.

The second case was that of a 68-year-old patient with diffuse atherosclerosis and a history of a Y-graft replacement of the infrarenal aorta as a result of an aneurysm some 15 years before, left-sided carotid endarterectomy performed 12 years previously, and combined coronary artery bypass grafting and a right-sided carotid endarterectomy performed 5 years before. Cardiac catheterization performed because of recurrent angina pectoris demonstrated progressive atherosclerotic disease of a graft to the left anterior descending coronary artery and of the native vessels, aortic valve stenosis with a mean gradient of 53 mm Hg, and a left ventricular ejection fraction of 0.30. The additional finding was an aneurysmal dilation of the descending thoracic aorta with a maximal diameter of 60 mm. After cardiac catheterization, progressive thrombocytopenia developed; this improved with heparin withdrawal. Heparin-induced thrombocytopenia type II was

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diagnosed by heparin-induced thrombocyte activation assay. The patient underwent combined reoperative coronary artery bypass grafting and aortic valve replacement. The operation was performed with recombinant hirudin as an anticoagulant for cardiopulmonary bypass. Two weeks after an uneventful operation and postoperative course he underwent an emergency operation because of rupture of the already known descending thoracic aneurysm. Total replacement of the descending thoracic aorta was performed with partial femorofemoral cardiopulmonary bypass and recombinant hirudin as an anticoagulant. He received in total 5 units of erythrocyte concentrates and 4 units of fresh-frozen plasma. The postoperative bleeding through the chest tube was 570 mL. The operation and the postoperative course were uneventful.

The same anticoagulant protocol was applied in both cases, as follows. Initially, recombinant hirudin (0.25 mg/kg body weight) was given intravenously as a bolus. Additional recombinant hirudin was given in the priming volume of the cardiopulmonary bypass at a dose of 0.20 mg/kg of body weight.[4] The levels of recombinant hirudin were measured in citrated whole blood with the TAS analyzer (Cardiovascular Diagnostics Inc, Raleigh, NC), and the cardiopulmonary bypass was started when the ecarin clotting time was longer than 400 seconds, which corresponded to a concentration of recombinant hirudin level in citrated whole blood of more than 4 μg/mL (Fig 1). During cardiopulmonary bypass, boluses of 10 mg recombinant hirudin were given intravenously to maintain a hirudin level in whole blood between 3 and 4 μg/mL (corresponding to an ecarin clotting time of 350-400 seconds). A 2,000,000 KIU (280 mg) dose of aprotinin was given as a short infusion before cardiopulmonary bypass and an additional 2,000,000 KIU aprotinin was added to the priming solution, followed by a continuous infusion of aprotinin at a dose of 500,000 KIU/h (70 mg/h) during cardiopulmonary bypass. After weaning from cardiopulmonary bypass, modified ultrafiltration was applied and a forced diuresis was stimulated with an intravenous infusion of 20 g mannitol, continuous infusion of dopamine (2 μg/kg of body weight), and 40-mg boluses of furosemide. The first clots were seen in the operating field within 30 minutes after the cessation of cardiopulmonary bypass. The postoperative anticoagulation regimen consisted of continuous infusion of recombinant hirudin to achieve a partial thromboplastin time of about 60 seconds.

Comment. Our report shows that extended operations on the aortic arch and descending thoracic aorta can be successfully performed in patients with heparin-induced thrombocytopenia by using recombinant hirudin as an anticoagulant. Alternative anticoagulant treatments include warfarin, ancrod, prostaglandins, and the heparinoid danaparoid sodium (Orgaran), which has some risk of immune cross reaction. We decided to use recombinant hirudin, a direct thrombin inhibitor, because it possesses some important advantages with respect to other alternatives, such as that subsequent normal anticoagulation can be achieved early after surgery because of its fast renal elimination (about 40 minutes in patients with normal renal excretion). It is necessary to emphasize that there is no antidote to hirudin and the reversal of the drug therefore requires clearance from plasma. It depends on normal renal function, with a rapid fall of the concentration at the end of the operation as assessed by means of the ecarin clotting time and plasma concentration of recombinant hirudin.

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