

A Report of Outcomes After Orthotopic Liver Transplant With Allografts From Heparin Antibody-Positive Donors

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Abstract

Heparin-induced thrombocytopenia (HIT) is an immune-mediated condition associated with thrombocytopenia and thrombotic complications. The condition is increasingly recognized in hospitalized patients including severely injured trauma patients. Because these patients may eventually be considered for organ donation, management of the HIT screen-positive donor has become an important issue in transplant surgery.

We describe the recent management of 2 liver allograft donors with relative thrombocytopenia and positive HIT antibody screens. In both cases, systemic anticoagulation at the organ recovery operation was accomplished with argatroban, a synthetic thrombin inhibitor. This management strategy resulted in successful transplants for 7 recipients (1 heart, 2 liver, 4 kidney). Neither of the liver recipients demonstrated signs or symptoms of HIT, and neither had any postoperative thrombotic complications. Based on this experience, a treatment algorithm for managing HIT-positive donors is proposed. In addition, the pathophysiology of HIT and various testing modalities for the disorder are discussed.

Key words: Liver allograft procurement, High-risk donors, Heparin-induced thrombocytopenia

Introduction

Currently, there are almost 17 000 patients with end-stage liver disease awaiting a liver transplant. In

2005, 6441 liver transplants were performed. [UNOS/OPTN Annual Report Data, www.optn.org] To partially relieve this organ shortage, the criteria for organ donation have been expanded. As the number and type of patients considered for liver allograft donation have grown, multiple new recipient and donor clinical issues are being considered. In many cases, these issues have the potential to contraindicate organ acceptance. Recently, our liver transplant program evaluated 2 donors with positive heparin-induced thrombocytopenia (HIT) antibody screening tests suspected of having HIT.

Heparin-induced thrombocytopenia is a rare coagulation disorder characterized by the development of thrombocytopenia (defined in this clinical situation as a reduction of more than 50%) (1) several days after exposure to unfractionated heparin or low molecular weight heparin. The pathogenesis of HIT involves the development of immunoglobulin G antibodies to the heparin-platelet factor 4 (pf4) complex (2, 3). In most cases, these antibodies develop idiosyncratically during exposure to heparin therapy. The heparin exposure that leads to the development of HIT can be minor, in the form of intravenous flushes, deep vein thrombosis prophylaxis, or indwelling heparin-coated catheters. In a subset of patients, HIT is associated with arterial and/or venous thrombotic complications (termed *HIT with thrombosis*).

Heparin-induced thrombocytopenia is increasingly being recognized in hospitalized patients, including in severely injured trauma patients (4, 5). It is estimated that 3% of patients receiving unfractionated heparin will develop antibodies to the heparin-pf4 complex (6). In the absence of re-exposure to heparin, the titers of these antibodies drop after 3 months and heparin can be safely reintroduced. If there is an indication for ongoing anticoagulation while high titers of antibody

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Experimental and Clinical Transplantation (2009) 1: 13-17

are circulating, alternative agents including argatroban, danaparoid, and lepirudin are recommended (7). In North America, argatroban is the only direct thrombin inhibitor licensed for the prophylaxis and treatment of patients with HIT or HIT with thrombosis. In Europe, clinicians may be more familiar with danaparoid and lepirudin.

The immunologic response associated with HIT has multiple potential ramifications for organ transplant recipients. Recipients with a history of heparin-pf4 complex antibodies are at risk for symptomatic disease recurrence if rechallenged with heparin during the perioperative transplant course. There are multiple reports documenting the management of these patients, including heart (8, 9), liver (10), renal (11), and stem cell recipients (12).

In contrast, the management of organ donors with HIT has not been well described. To prevent thrombosis in the donor organ microvasculature, systemic anticoagulation (typically accomplished with a bolus of intravenous heparin given immediately before aortic cross-clamping) is a requisite part of the organ recovery procedure. Presumably, giving a heparin bolus to a donor with circulating heparin-pf4 complex antibodies at the time of donor organ recovery could precipitate an acute thrombotic reaction in the donor organs, leading to early allograft dysfunction. Alternative systemic coagulation agents have been used in a variety of clinical settings for patients with HIT and HIT with thrombosis; however, their application to the donor recovery procedure has not been described.

The purpose of this report is to document the management strategy used during organ recovery, and the subsequent outcomes for 2 patients who received liver allografts from heparin-platelet 4 complex antibody-positive donors.

Case Reports

Patient A

Patient A was a 60-year-old man with end-stage liver disease from chronic hepatitis C virus infection. His model for end-stage liver disease score at the time of liver transplant was 29, and his relevant preoperative laboratory analyses included the following: serum total bilirubin 10.9 mg/dL, aspartate aminotransferase 59 U/L, alanine aminotransferase 26 U/L, alkaline phosphatase 59 U/L, creatinine 1.4 mg/dL, prothrombin time 23.2 sec, partial thrombo-

plastin time 61.6 sec, international normalized ratio 2.5, platelet count 56 000/ μ L. His blood type was O+, and he did not have a history of HIT. While he was an outpatient, an ABO identical liver allograft from a 20-year-old, 60-kg, female trauma patient, with a closed-head injury was allocated to him. The donor had been hospitalized for 6 days, during which time she developed thrombocytopenia (platelet count 302 000/ μ L $\rightarrow$ 80 000/ μ L). A heparin antibody screen had been obtained before organ allocation and resulted positive.

At organ recovery, the donor was hemodynamically stable with a normal appearing liver, a platelet count of 84 000/ μ L, and no evidence of thrombosis. Thoracic organs were not recovered owing to chest trauma. The donor underwent a routine liver and kidney allograft recovery with argatroban (200 mg) infused over 15 minutes immediately before aortic cross-clamping. The liver allograft was flushed in the donor operating room with a total of 8 liters of cold histidine-tryptophan-ketoglutarate solution (6L via an aortic cannula and 2L via a portal cannula on the back table), as well as 1 liter of cold lactated Ringers portal flush immediately before portal anastomosis in the recipient OR.

Before liver allograft implant, a back-table arterial reconstruction was required to anastomose a replaced right hepatic artery. The recipient operation was otherwise routine. The total cold ischemia time was 5 hours, 20 minutes. Intraoperatively, the patient's estimated blood loss was 4000 cc, and he required transfusion of 6 units packed red blood cells, 12 units fresh frozen plasma, 10 units of cryoprecipitate, and 12 units of platelets. After arterial reperfusion of the allograft, hemostasis was achieved, and the patient required no further transfusions.

Postoperatively, the international normalized ratio spontaneously corrected and the patient did well. Intravenous heparin was avoided in IV flushes, and he did not manifest any signs or symptoms of HIT, hypercoagulable state, or clotting disorder. The results of a heparin antibody assay obtained on postoperative day 14 were negative. His platelet count rose above 100 000/ μ L within 1 week of transplant, was 270 000/ μ L at discharge, and has remained in the normal range. It has now been 4 months since the transplant, and the patient has normal liver function and no thrombotic complications.

The kidney allografts from this donor were placed

into 2 recipients. United network for organ sharing (UNOS) records indicate that both kidney allografts had excellent initial function.

Patient B

Patient B was a 50-year-old woman with end-stage liver disease from chronic alcohol use. Her model for end-stage liver disease score at the time of transplant was 26, and her relevant preoperative laboratory values included the following: serum total bilirubin 31.5 mg/dL, aspartate aminotransferase 33 U/L, alanine aminotransferase 24 U/L, alkaline phosphatase 86 U/L, creatinine 0.6 mg/dL, prothrombin time 17.3 sec, partial thromboplastin time 35.1 sec, international normalized ratio 2.1, platelet count 27 000/ μ L. Her blood type was O+ and she did not have a history of HIT. While she was an outpatient, an ABO identical liver allograft from a 21-year-old, 65-kg, male trauma patient with a closed-head injury was allocated to her. The donor had been hospitalized for 9 days, during which time he developed thrombocytopenia (platelet count 177 000/ μ L $\rightarrow$ 74 000/ μ L). Before the organ offer, a heparin antibody screen was obtained and the result was positive.

At organ recovery, the donor was hemodynamically stable with a normal appearing liver, a platelet count of 75 000/ μ L, and no evidence of thrombosis. The donor underwent a routine heart, liver, and kidney allograft recovery with argatroban (200 mg) infused over 15 minutes immediately before aortic cross-clamping. The allograft was flushed in the donor operating room with a total of 8 liters of cold histidine-tryptophan-ketoglutarate solution (6 L via aortic canula and 2 L via portal cannula on the back table), as well as 1 liter of cold lactated Ringers portal flush immediately before portal anastomosis in the recipient OR.

The recipient operation was routine with a total cold ischemia time of 5 hours, 45 minutes. The patient had an intraoperative estimated blood loss of 1500 cc, and a transfusion requirement of 2 units of fresh frozen plasma. Postoperatively, the patient's international normalized ratio spontaneously corrected, and the patient did well. Intravenous heparin was avoided in intravenous flushes, and she did not manifest any signs or symptoms of HIT, hypercoagulable state, or clotting disorder. Her platelet count was 71 000/ μ L at discharge on postoperative day 7 and has remained above 100 000/ μ L since then. It has now been 8 months

since the transplant and the patient has normal liver function and no thrombotic complications.

The heart and kidney allografts from this donor were placed into 3 recipients. UNOS records indicate that the heart and both kidney allografts had excellent initial function.

Discussion

This report describes the strategy used to successfully transplant 2 patients with liver allografts from HIT screen-positive donors. These cases highlight several important features of HIT screen-positive donor management in the pretransplant setting. In most cases where critically ill patients develop thrombocytopenia, the test used to screen for heparin-pf4 complex antibodies is an enzyme-linked immunosorbent assay (ELISA). In both of the cases presented here, an ELISA test was used to screen the thrombocytopenic donors. The ELISA test is commonly used as an HIT screening modality because it is widely available, simple, and rapid. Although the sensitivity of these tests can be as high as 80%, their specificity is much lower (13, 14). Clinical predictors that estimate the pretest probability of HIT have been developed (15), however, the diagnosis of HIT can only be definitively ruled out with a negative functional assay such as the heparin-induced platelet aggregation test or serotonin release assay (13, 14, 16). These tests are more specific for heparin-induced platelet dysfunction, but are limited in availability by the requirement for specialized equipment and expertise (14). If available, these tests may prove a false-positive ELISA result and obviate consideration of alternative anticoagulation agents at the donor recovery operation.

The main reason to pursue a more specific assay is the cost difference between heparin (30 000 units = \$2.07) and argatroban (200 mg = \$873.39) [Internal pharmacy data]. Unfortunately, a functional assay is rarely ordered by the team caring for the patient before brain death and referral to the local organ procurement organization. As was the case with both of the donors reported here, usually there is insufficient time to process a functional HIT assay before the organ recovery operation.

In the absence of a negative functional assay result, the potential risks of argatroban administration must be weighed against the

potential that heparin-pf4 complex antibodies do exist and could cause catastrophic microvascular allograft thrombosis that would affect multiple organ recipients (15). Argatroban was chosen for our donors based on its availability and its safety record as an alternative anticoagulation agent in multiple posttransplant and nontransplant settings (17). The dosage of argatroban was determined by mimicking the recommended bolus dosing regimen for percutaneous coronary intervention in patients with HIT (350 mcg/kg) (18).

Adverse reactions to argatroban have been documented in the setting of continuous infusion and accidental overdose (19, 20). During transplant surgery, however, it is unlikely that clinically relevant amounts of argatroban would remain in the allograft after the flush procedure and be transferred to the recipient circulation upon allograft reperfusion. Theoretically, if argatroban did enter the recipient circulation, a self-limited coagulopathy could develop. Argatroban is metabolized by the liver with a half-life of residual argatroban in the recipient circulation of 45 to 60 minutes (21), but may be prolonged if early allograft dysfunction occurs (22). The level of argatroban effect can be measured with the partial thromboplastin time. In nontransplant patients, treatment of excess argatroban administration has included supportive care, hemodialysis, and administration of fresh frozen plasma (18-20). Use of activated prothrombin complex for this indication is controversial (23, 24).

Our experience with argatroban anticoagulation in 2 patients demonstrated no evidence of adverse complications. One of our 2 patients had a higher-than-usual blood product requirement. He entered the operation with an international normalized ratio of 2.5, and his clinical coagulopathy corrected shortly after allograft arterial reperfusion. While it is possible that residual argatroban flushed into the recipient at reperfusion contributed to this time-limited coagulopathy, our experience with patient B presented in this report (who had no postreperfusion clinical coagulopathy) suggests that the coagulation deficit observed in patient A was related to the patient's underlying liver disease-induced coagulopathy, and not the donor anticoagulation regimen. Ultimately, both recipients did well after liver transplant. Currently, each recipient has normal liver function and no evidence of thrombotic complications. Neither has required rehospitalization since the

transplant. In addition, based on the UNOS records available, there were no adverse effects from argatroban on the immediate allograft function of the 5 other allografts recovered from these 2 donors.

Although trauma and brain death are both associated with thrombocytopenia, without a functional heparin-induced platelet aggregation assay, it was impossible to determine if the ELISA screening tests used in the 2 donors reported here had produced a false-positive result. Likewise, in the other donors with positive HIT screening tests, it is unlikely that transplant clinicians will have complete data on the true status of heparin-pf4 complex antibodies at the time of allograft recovery. If time and resources permit, it is strongly recommended that the donor be tested with a functional HIT assay. In the absence of functional platelet aggregation data, the recommended management steps for donors with a positive heparin antibody screen and clinical suspicion of HIT are as follows: (1) avoidance of heparin in the donor; (2) use of argatroban (350 mcg/kg IV infused over 15 minutes) before aortic cross-clamp; (3) routine cold flush of the allograft; (4) avoidance of heparin in the recipient, (5) measurement of heparin antibody titers in the recipient within 48 hours after transplant.

Use of this algorithm has lead to successful transplants for 7 recipients with allografts from 2 donors that otherwise might have been refused for donation. Until larger studies determine the true incidence of HIT in HIT assay-positive donors, the outcomes observed in these 2 cases support the use of alternative anticoagulation agents as a means to accept organs from donors with positive heparin-PF4 antibody screens and clinical suspicion of the HIT syndrome.

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