Case Report:
Use of Bivalirudin to Prevent Thrombosis Following Orthotopic Liver Transplantation in a Patient with Budd-Chiari Syndrome and a History of Heparin-Induced Thrombocytopenia

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Abstract. Type II heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome that may arise in a time-dependent manner following heparin therapy, placing patients at significant risk for thromboembolic events. Therapy includes anticoagulation with a direct thrombin inhibitor and avoidance of heparin. We report a patient with Budd-Chiari syndrome and a history of heparin-induced thrombocytopenia who presented for orthotopic liver transplant and required postoperative anticoagulation with bivalirudin. During the post-transplant graft function improvement, we observed a significant dose-effect alteration manifested by an increased bivalirudin dose requirement as factor V activity increased. This observation is an important consideration in the attempt to maintain an optimal balance between effective anticoagulation and a reduced risk of postoperative bleeding.

Keywords: liver transplant, Budd-Chiari syndrome, thrombocytopenia, heparin, bivalirudin, thrombosis

Introduction

Type II heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome that may arise in a time-dependent manner following heparin therapy. The heparin-induced thrombocytopenia causes a hypercoaguable state, placing patients at significant risk for thromboembolic events [1,2]. Heparin-induced thrombocytopenia can be a common occurrence in surgical patients who receive unfractionated heparin therapy and it has been recognized extensively in the cardiac, vascular, and orthopedic surgery populations [3].

Management of HIT involves proper identification via clinical and laboratory indices, cessation of heparin and future avoidance of heparin in most clinical scenarios, initiation of a non-heparin anticoagulant alternative, and timely transition to oral vitamin K antagonist therapy once the platelet count has recovered. However, the appropriate management of a patient who requires future anticoagulation following completion of HIT therapy is controversial, especially in the post-operative setting.

We report a patient with Budd-Chiari syndrome and cirrhosis, with a past medical history significant for deep venous thrombosis (DVT) and HIT, who was admitted for an orthotopic liver transplant. Given the apparent hypercoagluability of this patient, he represented a significant risk for postoperative thrombosis. We address the post-operative management of this patient, highlighting the assessment of postoperative thrombosis risk, the selection of an anticoagulant agent given the patient’s past medical history, the intensity of anticoagulation that would provide efficacy at an acceptable risk of hemorrhage, and considerations for anticoagulation management with emphasis on appropriate dosing and titration in a patient with rapidly changing liver function.

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Case Report

Our patient was a 39-yr-old white male with Budd-Chiari syndrome. He was diagnosed with end-stage liver disease 2 yr prior to orthotopic liver transplant after presenting with cirrhosis, bleeding esophageal varices, and hepatic vein occlusion requiring placement of a mesocaval shunt. Low-dose unfractionated heparin was infused for 2 days following shunt placement at a dose of 300 units/hr. A hypercoagulability work-up performed on initial presentation was negative for deficiencies in protein C, protein S, or antithrombin III, presence of elevated antiphospholipid IgG and IgM antibody titers, factor V Leiden, prothrombin G20210 mutation, or lupus anticoagulant. However, a mildly elevated plasma homocysteine level of 17.7 µmol/L was noted.

The patient developed deep vein thrombosis (DVT) of the left lower extremity 11 days after unfractionated heparin was discontinued, requiring therapy to be restarted with an 80 unit/kg iv bolus dose followed by a continuous infusion of 18 units/kg/hr. A positive platelet factor 4 (PF4) ELISA assay (PF4 Enhanced, GTI, Waukesha, WI) was obtained during therapy, confirming the presence of anti-heparin-platelet factor 4 immunoglobulin and supporting the diagnosis of HIT. No significant drop in platelet count occurred during this time period, and the rationale for ordering a PF4 assay was based on the occurrence of thrombosis after heparin exposure. A 14C-serotonin release assay eventually resulted in an inconclusive or “borderline reaction.” Heparin therapy was replaced by lepirudin (Refludan, Berlex Laboratories, Wayne, NJ), a direct thrombin inhibitor (DTI). This agent was discontinued after 4 days due to the development of a left hemotorax that required a thoracotomy and evacuation. Further anticoagulation was deemed contraindicated at that time, and an inferior vena cava filter was placed. A PF4 assay obtained one year later was negative.

When the patient presented for liver transplant, a history of underlying hypercoaguability and hepatic vein outflow obstruction warranted consideration of post-operative anticoagulation in his management. A decision was made to anticoagulate postoperatively in an effort to reduce the
risk of thrombotic complication. Unfractionated heparin therapy for anticoagulation was avoided due to his history of HIT.

Bivalirudin (Angiomax, The Medicines Co., Parsippany, NJ) therapy was initiated postoperatively as a continuous iv infusion at 0.05 mg/kg/hr, with the goal of an activated partial thromboplastin time (aPTT) of 50 sec, approximately 1.5x baseline. Bivalirudin dose-titrations were made in 25 to 50% increments based on aPTTs measured every 6 hr. Dose requirements to maintain the goal aPTT are shown in Fig. 1. The bivalirudin dose required to achieve the goal aPTT increased significantly and consistently as the graft’s synthetic function improved, as measured by serial factor V assays (Fig. 2). On postoperative day 4, oral vitamin K antagonist therapy was initiated with warfarin to obtain a goal INR of 2 to 3 [3]. Bivalirudin was discontinued on postoperative day 7, with a final warfarin dose requirement of 5 mg/day.

Blood hemoglobin levels ranged from 8.4 to 11.4 g/dl and platelet counts ranged from 79,000 to 119,000/mm³ during DTI therapy. Renal function was stable throughout the treatment course with serum creatinine levels from 1.0 to 1.4 mg/dl. The patient was discharged on postoperative day 7. Follow-up 2.5 yr post-transplant shows the patient to be doing well and no longer requiring anticoagulant therapy.

Discussion

Budd-Chiari syndrome is a group of disorders that result from hepatic outflow obstruction involving the hepatic venules, large hepatic veins, or the right atrium [4]. Predisposing factors to Budd-Chiari syndrome include a myriad of inherited and acquired prothrombotic disorders that can be identified in about three-fourths of patients [4,5]. Of these prothrombotic conditions, myeloproliferative disorders are most commonly implicated [5]. Classifications of the syndrome include fulminant, acute, subacute, and chronic forms. Classification-specific symptoms range from hepatic encephalopathy to variable degrees of ascites and hepatic necrosis to cirrhosis with esophagogastric varices and splenomegaly. Abdominal pain and hepatomegaly are common to all classifications. Management options include medical treatment of ascites, anticoagulation, thrombolytic therapy with angioplasty, transjugular intrahepatic portosystemic

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**Fig. 2.** Factor V clotting assay as a measure of hepatic synthetic function following liver transplantation.
shunt placement, surgical shunting, and/or liver transplantation [4].

Thrombotic complications following orthotopic liver transplant are a significant source of morbidity and mortality in patients with or without known preoperative hypercoaguability. Hepatic artery thrombosis is the most common thrombotic complication, occurring in 2 to 12% of liver transplant recipients [6-9]. Venous complications, eg, occlusion or stenosis of the inferior vena cava, one or more of the hepatic veins, or the portal venous trunk, may also occur postoperatively. Technical errors, damage to the vascular endothelium during cannulation, or manipulation during previous procedures may play a role [10]. Disorders of hypercoaguability place postoperative liver transplant patients at increased risk for hepatic or portal venous thrombosis [5,10].

Our patient presented with bleeding esophageal varices, cirrhosis, and chronic hepatic venous outflow obstruction. He had a history of a left lower extremity DVT 11 days after a continuous infusion of unfractionated heparin, exhibiting a positive PF4 assay at that time. Given the patient’s medical course, it is likely that some degree of underlying thrombophilia existed despite a largely negative hypercoaguability work-up.

Postoperative lifelong anticoagulation is recommended following liver transplantation secondary to Budd-Chiari syndrome if the hypercoaguuble state is not corrected by the transplant alone [6,11]. A caveat to this may include postoperative management with hydroxyurea and aspirin in the setting of underlying myeloproliferative disease [12]. The unknown etiology of Budd-Chiari syndrome in our patient supported a decision to administer postoperative anticoagulation. Given a history of DVT associated with HIT syndrome, we were hesitant to rechallenge with unfractionated heparin despite a subsequently negative PF4 assay >100 days later. In most situations, future avoidance of heparin would be indicated in a patient who develops HIT. On the contrary, a one-time, intra-operative heparin administration for cardiac or vascular surgery procedures may be warranted in a patient with a history of HIT, but documented heparin-antibody negativity >100 days following the initial positive assay [3]. Direct thrombin inhibition would then replace heparinization following completion of the procedure. In our patient, risk vs benefit considerations favored postoperative anticoagulation with a DTI, given the desire to avoid post-surgical thromboembolic complications and the need for a multiple-day course of parenteral anticoagulation following surgery until adequate anticoagulation with warfarin could be achieved.

Three DTI agents are available for systemic, full-dose anticoagulation in patients where unfractionated heparin or low-molecular-weight heparin therapy is contraindicated. They include Argatroban (GlaxoSmithKline, Research Triangle Park, NC), lepirudin, and bivalirudin. All 3 agents are potent inhibitors of free and clot-bound thrombin, require no cofactors for function, and have no antidote for reversal. The 3 DTIs exhibit different pharmacokinetic profiles, mandating careful agent selection based on patient-specific organ function. Lepirudin is primarily eliminated by renal mechanisms. The terminal half-life is 1.1 to 2 hr, but may be prolonged to 2 days during renal failure [12,13]. This is cause for extremely vigilant monitoring and dose reductions in patients with renal insufficiency. Bivalirudin is eliminated by a combination of intravascular proteolytic cleavage (80%) and renal excretion (20%). The elimination half-life ranges from 25 min in patients with normal renal function, to 57 min in severe renal impairment, to 3.5 hr in hemodialysis-dependent patients off dialysis [14]. Close monitoring and dose reductions are required in patients with renal impairment; however, there should be no effect on elimination in patients with isolated hepatic dysfunction. Argatroban undergoes hepatic metabolism with excretion primarily in the feces, exhibiting a half-life of 39 to 51 min. Minor renal elimination exists. In patients with hepatic impairment, the half-life is prolonged requiring a decrease in dose [15].

Bivalirudin was chosen because of its short half-life and reliance on proteolytic and renal elimination mechanisms as a primary pathway for clearance, independent of the need for hepatic metabolism. The shorter half-life allows easier titration and faster elimination should a bleeding complication arise. We chose a goal aPTT of approximately 1.5x baseline, or approximately 50...
sec, to provide a satisfactory level of post-transplant anticoagulation with acceptable risk of postoperative hemorrhage.

A patient in the postoperative period following liver transplantation undergoes drastic changes in the ability to synthesize proteins such as albumin and coagulation factors, transitioning from a state devoid of synthetic ability to a fully functioning graft. Factor V clotting assays may be obtained in the postoperative setting as a surrogate parameter to monitor protein synthetic function. Prothrombin, the precursor protein of thrombin, is synthesized exclusively by the liver along with the other vitamin K-dependent coagulation factors and should increase in concentration as graft function improves. This would result in a shortening of aPTT, the global clotting assay used to indirectly measure the concentration of all the coagulation factors involved in the intrinsic and common pathways of the clotting cascade. The increased synthesis of these coagulation proteins postoperatively creates a situation where the dosing requirement of a DTI is directly impacted, as illustrated in Figs. 1 and 2. We initiated bivalirudin at 0.05 mg/kg/hr, a 75% dose reduction from the typical starting dose with normal renal function. Postoperatively, we observed that the dose required to achieve our goal aPTT consistently increased as the synthetic function of the graft represented by serial factor V assays returned to normal. It appears that rising factor V activity may even precede the requirement for bivalirudin dosage adjustments based on observed aPTT, indicating that an aspect of predictability may be present. By the conclusion of the bivalirudin continuous infusion, the infusion rate had been gradually increased to 0.24 mg/kg/hr, a 5-fold increase in dose.

The significance of this observation is that the dose requirement for bivalirudin steadily increased independent of any pharmacokinetic effect. In other words, a greater bivalirudin dose and serum concentration appeared necessary to achieve the desired target aPTT due to progressively increased hepatic synthesis of coagulation factors, rather than a greater dose to maintain therapeutic serum concentrations of the agent, as the liver is not a factor in bivalirudin elimination. This greatly impacts the ability of the clinician to maintain adequate levels of anticoagulation while avoiding bleeding complications that could arise from DTI overdose. Full attention should be paid to the dynamic balance of the graft's functional capacity and synthetic deficiency early on in the postoperative period.

A cirrhotic patient with deficient factor production requiring direct thrombin inhibition for HIT may also have lower dosage requirements of bivalirudin. However, such a patient would likely be at a steady state that would translate into a consistent serum bivalirudin level and bivalirudin dose. In our patient, the status of the patient's functional ability to synthesize coagulation factors was improving, likely translating to an increased bivalirudin dose requirement to achieve goal anticoagulation.

This case represents a situation where organ function requires consideration for reasons other than elimination of drug. The observed pharmacodynamic effect caused by the graft's heightened ability to synthesize coagulation factors appears to be responsible for an increase in the effective dose required to maintain adequate anticoagulation. It is likely that this effect would be seen with heparin or one of the other direct thrombin inhibitors, though no such case has been described.

In summary, post-transplant anticoagulation is sometimes required, as in the case of liver failure secondary to Budd-Chiari syndrome. Rarely, a contraindication to heparin may be present, requiring the use of a DTI. Dose requirements may vary greatly between the immediate postoperative period and when the graft regains synthetic function. Conservative initiation of direct thrombin inhibition may be required early on. However, vigilant and frequent monitoring of aPTTs should be conducted so that the balance of effective anticoagulation and reduced risk of bleeding can be optimized.

References


