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Increased risk of vascular thrombosis in pediatric liver transplant recipients with thrombophilia

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ABSTRACT

Background: Pediatric patients who undergo liver transplantation are at higher risk of developing vascular complications when compared to adult liver transplant recipients. The consequences of hepatic artery thrombosis (HAT) or portal vein thrombosis (PVT) can cause significant morbidity and mortality. We examined pediatric liver transplant recipients who developed vascular thrombosis and the presence of thrombophilia.

Methods: We examined outcome in all pediatric patients who underwent liver transplantation. Recipient, donor demographic data, and outcome data were examined. Categorical differences were compared using the unpaired Student t-test and nominal variables using either the chi-square or the Fischer exact test. A P value of <0.05 was considered significant.

Results: Forty-six pediatric patients underwent liver transplantation. Twenty-one recipients were found to have thrombophilia, including 5 with HAT and 2 with PVT. When comparing recipients with or without any vascular thrombosis, those with thrombophilia had a significantly higher incidence of developing a vascular thrombosis (7/21 *versus* 0/25, $P = 0.0017$). Five of 42 recipients with artery-to-artery reconstruction developed HAT *versus* 0 of 4 with a conduit. Recipients who developed any thrombosis were significantly lower in weight than those who did not develop any thrombosis (9.0 ± 1.6 kg *versus* 22.2 ± 16.0 kg, $P = 0.0366$).

Conclusions: All pediatric liver transplant recipients who developed any vascular thrombosis were also found to have thrombophilia. Recipients who were smaller in size were at significantly higher risk of developing vascular thrombosis. Lower weight recipients with thrombophilia may benefit from arterial reconstruction with a conduit to decrease the risk of vascular thrombosis.

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1. Introduction

Pediatric patients who undergo liver transplantation are at higher risk of developing vascular complications, particularly hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT), when compared to adult liver transplant recipients [1–4]. HAT and PVT are associated with significant morbidity, including the need for anastomotic revision and reconstruction, graft loss, retransplantation, and increased mortality [1,4–7]. The incidences of HAT and PVT as reported in the pediatric liver transplant literature are variable and can be up to 25% and 33%, respectively [5,8]. Several factors identified to be statistically significant predictors for these devastating complications include smaller vessel sizes, graft-recipient weight disparities, prolonged cold-ischemia time, CMV infection, acute rejection, perioperative fresh frozen plasma transfusions, elevated posttransplant hematocrit levels, and the lack of a posttransplant prophylactic anticoagulant treatment [3,8–13]. To date, however, there have been no studies examining recipient thrombophilia as a separate risk factor for thrombotic complications in pediatric liver recipients. Previous studies in the renal transplant literature [14,15] have shown that renal transplant recipients with a thrombophilia may have an increased incidence of rejection. We also examined if presence of a thrombophilia was associated with an increased risk of rejection in this patient population.

The aim of this study was to determine the frequency of thrombotic complications in pediatric patients undergoing deceased donor liver transplantation at our center and to examine the relationship between the incidence of either HAT or PVT and the presence of thrombophilia.

2. Methods

A retrospective chart review of all patients who underwent liver transplantation from January 1, 2010 to July 31, 2014 at our institution was performed. The dates were chosen to ensure the current group of transplant surgeons was involved in the uniform management of the patients. Medical charts were reviewed for recipient and donor demographic data including age, race, sex, weight, and blood type. Outcome data were also reviewed and included cold storage time (time from donor aortic cross clamp to liver out of ice) in minutes, anastomotic time (out of ice time to unclamping of portal vein) in minutes, estimated blood loss at transplant, intraoperative transfusion requirement, presence and number of rejections, graft survival, mode of arterial anastomosis (artery-to-artery *versus* conduit), HAT, and PVT.

HAT and PVT were diagnosed either intraoperatively by clinical findings or use of a Doppler probe or postoperatively with Doppler ultrasound. The surgical technique used was hepatectomy without vena cava preservation. Arterial reconstruction was either to the recipient's native hepatic artery or to the aorta with the use of a supraceliac or infrarenal arterial conduit created from the donor iliac artery. Criteria to use any type of conduit were based upon the quality of the artery as determined by surgeon judgment (i.e., presence of intimal dissection) or anatomic issues (i.e., repeat liver transplant). Risks associated with reconstruction with a conduit were the potential for increased blood loss, operative time, and reduction of blood flow to the kidneys during aortic cross clamping. Biliary reconstruction was performed either with a choledochocholedochostomy or with a Roux-en-Y choledochojejunostomy.

The presence of thrombophilia was diagnosed using our institution's laboratory panel that tested for the presence and activity levels of Protein C, Protein S, antithrombin III, and factor VIII. The panel also included assays for Factor V Leiden, anticardiolipin antibody, lupus anticoagulant, prothrombin gene mutation, homocysteinemia, antinuclear antibodies, methylenetetrahydrofolate reductase mutation, and heparin-induced platelet aggregation. Patients were tested preoperatively for thrombophilia if risk factors were present, including but not limited to personal or family history of thrombosis, and tested postoperatively if a thrombotic event occurred.

Our institution's posttransplant anticoagulation and antithrombotic regimen consisted of a continuous infusion of dextran 40 for the first 5 postoperative days which was initiated once the international normalized ratio was less than 2. Based on the surgeon's judgment, heparin therapy was also initiated, titrating to keep the PTT about 60 s. After completion of the dextran, acetylsalicylic acid and dipyridamole were initiated on postoperative day 5. In patients where heparin had been initiated, the patient was started on warfarin for long-term anticoagulation. If the antithrombin III levels were found to be low, a dose was also administered in the early postoperative period. Patients with known thrombophilia preoperatively were not prophylactically treated with anticoagulation preoperatively; based on surgeon judgment, heparin was used postoperatively in addition to the previously mentioned anticoagulation protocol.

Immunosuppression therapy consisted of methylprednisolone for induction and tacrolimus and prednisolone for maintenance immunosuppression. Mycophenolate mofetil was added if a patient had multiple rejection episodes.

Data were entered into a relational database (Stat View 5.0, SAS Institution, Cary, NC). Differences were compared using the unpaired Student *t*-test for categorical variables and either the Chi-square or the Fischer's exact test for nominal variables. A *P*-value of <0.05 was considered significant. Institutional Review Board approval was obtained for this study.

3. Results

Between January 2010 and July 2014, 46 pediatric patients underwent liver transplantation. All but one of the liver grafts was a deceased donor whole graft. One transplantation procedure took place using a split graft (left lateral lobe). Diagnoses of the recipients are listed in Table 1. The most common diagnoses of patients undergoing liver transplantation included biliary atresia (37%), followed by fulminant hepatic failure (26%) and tumors (20%). Table 2 summarizes the donor and recipient demographic data. Twenty-one recipients were found to have thrombophilia, including five with HAT and two with PVT. The types and