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Liver Doppler findings in pediatric patients after Total Pancreatectomy and Islet Autotransplantation

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Abstract

Objective—This study is intended to establish normal values for velocities in the hepatic artery and portal veins in pediatric patients after Total pancreatectomy and islet autotransplantation.

Methods—A retrospective review was performed of liver Doppler studies in pediatric patients after TPIAT over 6 years at an academic children's hospital. Doppler velocities in the liver vasculature and hepatic artery resistive index (RI) were recorded.

Results—65 pediatric patients were evaluated. There were no cases of portal vein thrombosis or other hepatic vascular complications. The average hepatic artery peak systolic velocity was 158 cm/s (standard error 60.9), with an average RI of 0.57 (standard error 0.09). The average main portal vein velocity was 32 cm/s (standard error 12.9).

Conclusion—Portal vein thrombosis is rare in pediatric patients after TPIAT. A wide range of hepatic artery and portal vein velocities are encountered in children immediately after TPIAT without hepatic vascular complications and can be considered normal.

Keywords

Islet Autotransplantation; islet cell; Doppler; pancreatectomy; pancreatitis

Introduction

Total pancreatectomy and islet autotransplantation (TPIAT) has become an option for pain management in pediatric patients with chronic or hereditary pancreatitis which is refractory to medical management [1-5]. Pediatric patients with chronic pancreatitis are at risk for decreased quality of life due to pain, frequent hospitalizations, missed days of school, and narcotic dependence [3,6]. The overall incidence of chronic pancreatitis is 0.2-0.6% in the United States [7, 8]. The most common causes of chronic pancreatitis in children are

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hereditary/genetic and idiopathic pancreatitis [5, 9-10]. The PRSS1, CFTR and SPINK1 genes are associated with childhood chronic pancreatitis [11-12]. Chinnakotla et al. found hereditary/genetic causes to be the most prevalent cause of pancreatitis in pediatric TPIAT patients, representing 68.1% of cases [2]. When imaging a patient with hereditary pancreatitis, one may encounter a pediatric patient with a parent who has already undergone TPIAT or sibling who is facing TPIAT in the future. Overall, pediatric TPIAT patients do better than their adult counterparts, with lower insulin dependence, less opioid use and higher quality of life scores [1-2, 13]. Despite better outcomes, pediatric TPIAT patients may still suffer post-operative pain and hyperalgesia from central sensitization and discomfort from intestinal dysmotility [2] which can lead to further diagnostic imaging.

TPIAT was first performed in adult patients in 1977 with pediatric TPIAT reported in 1989 [2,14]. Prior to TPIAT all patients at our hospital are evaluated by a team of pediatric specialists including surgeons, gastroenterologists, and endocrinologists. The procedure typically consists of a total pancreatectomy, pylorus sparing segmental duodenectomy, enteric-biliary reconstruction with Roux-en-y duodenojejunostomy, splenectomy, and cholecystectomy, along with islet cell purification and subsequent infusion into the portal system. In addition, our patient population typically has concurrent gastrojejunostomy tube placement (Stamm technique) to allow for early enteral feeding [6]. To decrease risk of portal vein thrombosis, care is taken to frequently monitor portal pressures during islet cell infusion and to stay within a safe portal infusion pressure. Postoperatively, these patients are anticoagulated with Dextran 40 for the first 48 hours and heparin for one week. Aspirin is also used to prevent thrombosis starting 48 hours after TPIAT [3]. In addition to anticoagulation, these patients are treated with prophylactic antibiotics which are adjusted according to the results of pancreatic cultures obtained at the time of islet cell harvest. In the absence of functioning islet cells, post TPIAT patients require close blood sugar management, initially accomplished through IV dextrose infusion. Enteral feedings provide a more predictable blood sugar response and are started on postoperative day two at a rate of a few milliliters per hour with a goal of reaching full enteral feeding within a week. Gastroparesis is common and prevents per oral feeding in the early postoperative course.

The current post-TPIAT imaging protocol at our hospital includes liver Doppler studies on postoperative days 1 and 7 [3]. Doppler ultrasound has a negative predictive value of 0.98 making it the non-invasive test of choice for patency of the liver vasculature [14, 15]. To the best of our knowledge no study has established the expected Doppler findings for pediatric patients after TPIAT. This study is intended to establish normal values for velocities in the hepatic artery and portal vein in pediatric patients after TPIAT, and to determine the rate of hepatic vascular complications in these patients.

Materials and Methods

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by University of Minnesota Institutional Review Board. Parent, guardian or next of kin consent was not required for the minors because a waiver of consent was obtained. The waiver of consent was obtained because the research involves no more than minimal risk. The waiver does not adversely affect the rights and welfare of the participants.

The subjects for this retrospective review included patients under the age of 18 years who underwent TPIAT at an academic pediatric hospital between February 2010 and February 2016 and had liver Doppler studies during their postoperative stay. One patient was excluded due to a signed statement in the medical record indicating that the patient was not to be included in any research studies. All liver Doppler ultrasound examinations performed during the inpatient stay following TPIAT were reviewed. The ultrasound studies were performed by American Registry of Radiologic Technologists (AART) certified ultrasound technologists with Philips IU22 ultrasound machines (Philips Healthcare, Best, The Netherlands) using curved 5-2MHz and 5-1MHz probes. Fellowship trained pediatric radiologists with 6 and 10 years of post-fellowship experience reviewed the Doppler images. Doppler velocities (with angle correction of 40 to 60 degrees) in the extrahepatic portion of the main portal vein, right and left central branch portal veins and extrahepatic proper hepatic artery were recorded. Hepatic artery resistive index and patency of flow within the hepatic veins were also recorded. The portal vein and hepatic artery were interrogated just outside of the liver hilum. The portal vein branches were interrogated just beyond the bifurcation of the main portal vein. Patients were maintained nil per os (NPO) during their ultrasound examinations. However, no adjustments were made to their normal rate of continuous jejunal tube feedings. The patients' imaging and medical record were reviewed for postoperative hepatic vascular complications, such as acute portal venous thrombosis and for other complications such as intra-abdominal infections that could have an effect on liver Doppler findings. Patients were considered to have an infection that could alter their Doppler study if their infectious symptoms were documented as occurring within 48 hours of their Doppler study. Islet cell culture positivity alone was not included as an infection.

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA). Graphs were plotted in R (<http://www.r-project.org>). The trend over time for Doppler outcomes was examined using linear mixed model to account for within-patients correlation. In an exploratory analysis, abdominal infection was adjusted in the model. However, it did not show statistically significant association with Doppler measurements, and was not included in the final model. The estimated mean and standard error (SE) at each post-transplant day were reported and plotted. Different days were compared pairwise, and multiple comparison was adjusted using Tukey's method. Doppler measurements between patient groups with and without abdominal infection at each day were also compared, and p-value was calculated by Wilcoxon rank test. P-value less than 0.05 is considered as statistical significance.

Results

70 pediatric patients underwent TPIAT during the study time frame. Five (7.1%) patients had no postoperative liver Doppler evaluation and were excluded. The patients who did not have postoperative liver Doppler US were greater than 10 years of age (average 14.7 years of age). One of the excluded patients underwent TPIAT, but had the islet cells placed into the peritoneum (rather than the portal system) due to hepatic fibrosis. Two other excluded patients were re-operated on in the first few days after TPIAT. One of these two patients was evaluated with computed tomography (CT) with intravenous contrast due to acute clinical

deterioration prior to returning to the operating room. The other four excluded patients had no cross-sectional imaging during their hospitalization.

The remaining 65 pediatric patients had a total of 128 liver Doppler studies which were evaluated. Patient ages ranged from 3.1 years to 17.7 years and the average age at transplant was 11.6 years. There were 37 (56.9%) female and 28 (43.1%) male patients. Of the 128 Doppler studies, 75 (58.6%) were performed on female patients, and 53 (41.4%) were performed on male patients. There were no cases of acute portal vein thrombosis or other hepatic vascular complications. Two patients were known to have partial portal vein thrombosis prior to TPIAT, which resolved with treatment prior to the procedure.

Patients received their first liver Doppler study on postoperative days 0-2. Forty-nine (75.4%) of the patients had repeat liver Doppler examinations. The first follow up US was performed on postoperative day 1 in 12.2%, day 2 in 6.1%, day 3 in 4%, day 4 in 12.2%, day 5 in 0%, day 6 in 20.4%, day 7 in 36.7%, day 8 in 4.1% and day 9 in 4.1%. Eight patients had a third US (performed on postoperative day 2-8). Three patients had more than 3 US studies each (the maximum was six studies in one patient). In two of these three patients there were elevated portal infusion pressures during islet cell infusion which caused concern for possible intraoperative portal vein thrombosis. The third patient had chylous ascites which resolved. No patient developed portal vein thrombosis in the postoperative period. The distribution of liver Doppler studies by postoperative days is seen in figure 1, with the greatest number of examinations occurring on postoperative days 1 and 7. Patients averaged 2 liver Doppler examinations each.

The average hepatic artery peak systolic velocity was 157.6 cm/s (SE 60.9 cm/s) with a range of 57-369 cm/s. The mean hepatic artery RI was 0.57 (SE 0.09) with a range of 0.35-0.85. The average hepatic artery peak systolic velocity in patients who underwent additional liver Doppler examinations was 182 cm/s, while the average peak systolic hepatic artery velocity of patients who were only imaged once was 174 cm/s. The mean main portal vein velocity was 31.9 cm/s (SE 12.9) with a range of 12-84 cm/s. The mean right portal vein velocity was 21.9 cm/s (SE 9.4 cm/s) with a range of 7-65 cm/s. The mean left portal vein velocity was 17.4 cm/s (SE 7.9 cm/s) with a range of 7-49 cm/s. The mean main portal vein velocities peaked on postoperative day 7 (figure 2) while hepatic artery velocities trended down over time (figure 3). Hepatic artery resistive indices trended slightly up over time, but the relationship was less linear (figure 4).

Nine (13.8%) patients had an established intraabdominal infection at the time of their Doppler US examinations. Eight patients developed infection greater than two days after their last liver Doppler examination resulting in a total of 17 (26.2%) patients with an intraabdominal infection during their postoperative hospitalization. When comparing actively infected (n=9) and non-infected (n = 56) groups there was no significant difference in hepatic artery peak systolic velocity (p-value = 0.887), hepatic artery resistive index (p-value= 0.432), or main portal vein velocity (p-value = 0.467).

Discussion

Thomas et al. found an adult rate of portal vein thrombosis after TPIAT of 1 in 107 cases (0.9%) [17]. Wilhelm et al. showed portal thrombosis rate correlated to older patient age and increased portal pressure with partial portal vein thrombosis occurring in 8 of 233 patients (3.4%) [18]. There were no instances of acute portal vein thrombosis in our study population of 65 pediatric patients. Current islet autotransplant technique with limits on total injected graft volume, careful management of islet cell infusion pressure, and postoperative anticoagulation likely contribute to the absence of portal vein thrombosis in our study population [3,18]. In this study there was one patient with superior mesenteric vein thrombosis secondary to a segmental small bowel volvulus, which was found by computed tomography (CT) and confirmed at surgery. No other vascular complications were encountered in the study. However, the mean main portal vein velocities trended upward over time, while hepatic artery velocities trended down over time. This may be due to microvascular occlusion in the portal veins due to the infused islet cells, and vasodilatation in the hepatic arteries, which would compensate for diminished portal flow, and lower the hepatic artery resistive index. Clearing of microvascular portal occlusions over time would account for the Doppler trends seen in this study and suggests that Doppler evaluation is indeed necessary in the immediate postoperative period, as main and branch portal vein thrombosis remains a theoretical risk.

Portal venous blood flow has been shown to increase in response to oral feeding [19, 20]. The patients in this study received continuous enteral feedings starting at a rate of a few milliliters per hour on postoperative day 2. The rate of continuous enteral feeding is increased slowly, per patient tolerance, with a goal of full enteral feeds around postoperative day 7. This increase in enteral feeding volume could also contribute to Doppler trends of increasing portal blood flow and decreasing hepatic arterial velocities seen in this study.

Limitations in our study include that it is a single institution, retrospective review without a comparison population with portal thromboses or other liver vascular complications. An additional limitation of this study is the absence of preoperative liver Doppler imaging for comparison. Pre-operative evaluation in these patients consists of either computed tomography or magnetic resonance imaging often performed outside of our system.

Nonvascular complications have been reported in children in the postoperative period after TPIAT. Chinnakotla et al. found an in-hospital mortality of 1.3% in pediatric TPIAT [3]. Infection is a potential complication after TPIAT in pediatric patients. Berger et al. found a post-operative infection rate of 47.7% in the first six months following TPIAT, comprised mostly commonly of surgical site infections [6]. This study found a smaller rate of postoperative infections (26.2%), likely due to a shorter timeframe and a study end point of initial discharge from the hospital. Active abdominal infection did not have a significant effect on the liver Doppler velocities. Infrequent deaths due to infection were reported in pediatric patients long after TPIAT leading to post-splenectomy antibiotic prophylaxis [3]. A recent study by Bellin et al. found that gastrojejunostomy tube complications were the most frequent category of complication in younger children post-TPIAT [13]. Given the lack of reported PV thrombosis in pediatric patients after TPIAT and the reported bowel and

infectious complications, we suggest that complete abdominal imaging is necessary to assess the cause of acute post-operative deterioration in these patients.

In conclusion, wide ranges of hepatic artery and portal vein velocities are encountered in children immediately after TPIAT without hepatic vascular complications and can be considered normal. Liver Doppler remains a necessary part of post-operative care for pediatric TPIAT patients given portal vein thromboses reported in adults. However, repeat US examination based only on portal vein velocities or hepatic artery resistive indices is likely unnecessary. The need for repeat Doppler ultrasound evaluation should be based on clinical findings or concerns such as elevated portal pressures during islet cell infusion, or a history of prior portal thrombus. These patients will likely be followed closely with liver Doppler after TPIAT. For patients without these types of concerns we propose a conservative range of normal values representing 1 SE from the mean for each of the Doppler measurements. For clinically stable pediatric TPIAT patients, hepatic artery peak systolic velocities of 97-219 cm/s, hepatic artery resistive indices of 0.48-0.66 and main portal vein velocities of 19- 45 cm/s can be considered normal and do not warrant follow up Doppler evaluation.

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Figure 1.
Distribution of liver Doppler studies by postoperative day

Figure 2.
Main portal vein mean velocity in cm/sec versus postoperative day

Figure 3.
Main Hepatic Artery peak systolic velocity in cm/sec versus postoperative day

Figure 4.
Main Hepatic artery RI versus postoperative day