Early hepatic arterial thrombosis after pediatric living donor liver transplantation: a single-center experience

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To the Editor: As one of the most severe vascular complications after liver transplantation (LT), early hepatic arterial thrombosis (eHAT) may lead to ischemic liver necrosis and ischemic biliary tract complications such as biliary leakage and eventually graft or patient loss.[1] The outcome, however, can be significantly improved by early diagnosis and intervention.[2] Satisfying intervention is achieved by revascularization, when it fails, life-saving retransplantation must be considered. Given that retransplantation is not always available because of the poor graft pool especially in eastern countries,[1] every LT center should devote to reduce the incidence of eHAT.

We collected and analyzed the information and characteristics of patients who received pediatric living donor LT (pLDLT) from January 2015 to January 2019; 3 cases among 278 cases of pLDLT developed eHAT. The most common indication for pLDLT was decompensated liver cirrhosis caused by biliary atresia (67.6%), congenital metabolic disease (29.1%), liver failure, and other reasons (3.2%) [Table 1].

The three patients who developed eHAT were diagnosed on post-operative days 2, 4, and 9, respectively. Abnormal hepatic arterial blood flow was discovered by Doppler ultrasonography (DUS) first. One case was diagnosed by the contrast-enhanced ultrasonography and the other two by DUS. The average time of diagnosis of eHAT was post-operative day 5 (days 2, 4, 9). One patient died of cardiac insufficiency on post-operative day 16, although her liver function remained normal before death. The other two cases with eHAT underwent thrombectomy and reanastomosis immediately after the complication was confirmed. Small hypoechoic foci within the hepatic parenchyma were discovered in one patient by DUS on post-operative day 60, and elevated transaminase was also detected for about 2 weeks. The other patient, however, remained in a stable condition. Follow-up observation of these two patients was maintained for 2 and 4 years, with no long-term complications observed.

Compared to the studies published in the 1980s, the incidence of eHAT is lowered in the latest studies. The meta-analysis published in 2009 reported that the incidence of HAT from 1993 to 2006 decreased to 3.8%.[3] A study in 2017 showed no HAT in 440 cases of pLDLT.[4] These good outcomes are due to the progress made in surgical techniques.

In one of the largest reports published by Uchida *et al*[2], female sex and low body weight were risk factors in univariate analysis. Li *et al*[5] reported that graft weight recipient weight ratio (GWRW) >4% was a risk factor of developing HAT, and Uchida *et al*[2] also considered higher GWRW to be a risk factor, and the median GWRW of patients who developed HAT was 3.16%. We tend to set the cut-off ratio at GWRW of 5%. The graft volume was calculated before every pLDLT operation, and if GWRW was predicted to be >5%, a size-reduced transplant was implemented. Based on our experience, transplantation of monosegment graft is preferable to simple size-reduced LT under the circumstance in which GWRW is >5% and the ratio of the anteroposterior diameter of the graft to that of the recipient's abdominal cavity is >1.5. Too thick a graft can lead to difficult abdominal closure and pressure against the anastomosed vessel, which may contribute to the increased incidence of HAT and portal vein thrombosis.[2]

Under the circumstance when the multibranched hepatic artery is discovered, the middle hepatic artery arises from the right hepatic artery, or the arteries of segments S2–S4

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Table 1: Overall summary of the clinical characteristics of the patients with eHAT.

Case No.	Indication for LDLT	Sex	Age (months)	Bodyweight (kg)	GWRW (%)	Previous operation history	Biliary anastomosis fashion	Graft type	Operation time (min)	Day of eHAT	Treatment	Outcome
1	Decompensated liver cirrhosis secondary to BA	Female	8	7	4.0	Non	HJ	LLL	455	Day 9	–	Died at post-operative day 16
2	Decompensated liver cirrhosis secondary to BA	Male	8	7	2.8	Diagnostic bile duct exploration	HJ	LLL	515	Day 4	Immediate thrombectomy and reanastomosis	Alive without late complications
3	Decompensated liver cirrhosis secondary to BA	Female	6	6	4.2	Diagnostic bile duct exploration	HJ	LLL	375	Day 2	Immediate thrombectomy and reanastomosis	Alive without late complications

BA: Biliary atresia; eHAT: Early hepatic arterial thrombosis; GWRW: Graft weight recipient weight ratio; HJ: Roux-en-Y hepaticojejunostomy; LDLT: Living donor liver transplantation; LLL: Left lateral lobe.

have separate origins, we tend to implement multiple anastomoses. Even though adequate blood flow from the middle hepatic artery may be achieved by anastomosis of the left hepatic artery alone, multiple anastomoses are also the optimal choice. It is generally believed that the graft bile ducts obtain their blood supply exclusively from the hepatic arterial blood flow; thus, we suggest that the blood supply of the recipients' biliary duct can benefit from multiple hepatic arterial anastomoses.

Arterial anastomoses can be difficult when multiple anastomoses are inevitable. That is when interposition vascular grafts are needed. Although interposition grafts and dual arterial anastomoses are considered as risk factors for HAT development, Mehta *et al*[1] reported successful implementation of dual arterial anastomoses in LDLT and no patients aged <1 year developed HAT. Lee *et al*[6] reported the use of great saphenous vein conduits as interposition grafts with encouraging results. In a prior study published by our center, we shared our experience with the use of REGA as an interposition graft in recipients with metabolic diseases because the diameter of REGA is matchable with the diameter of the hepatic artery.[7]

ABO-incompatible transplantation is considered an independent risk factor for pLDLT.[2] Eight patients underwent ABO-incompatible LT in our study, none of them developed vascular complications. Massive blood product infusion associated with ABO-incompatible LT remains a risk factor, but with proper perioperative management, the related vascular complications can be minimized.

We analyzed factors that are considered to be high risk, but none of these factors reached statistical significance.

We suggest that a designated surgeon experienced in microsurgical techniques should complete the arterial anastomotic procedure. A three-point interrupted method (interval angle 120°) is preferred because of its accuracy while suturing. Excessive pulling during hepatic dissection or arterial anastomosis should also be avoided to maintain intimal integrity. The diameter of the two ends should be matchable, and interposition vessel grafts should be considered when necessary. The diameter of the arteries usually ranges from 1 to 3 mm; therefore, a 2.5 or 5.0× magnification loupe should be sufficient. It is reported that hepatic artery diameter <3 mm is a risk factor, but we believe that with the progress made in microsurgical techniques, this problem has been overcome. Lin *et al*[8] reported a low incidence of HAT using a 6 to 15× magnification microscope while anastomosing the hepatic artery and described using loupes or a smaller microscope (<6×) to anastomose vessels <2 mm as a risk factor. Compared to using loupes, using microscopes means a limited field of vision and prolonged operation time. Other authors have supported the benefit of using loupes instead of microscopes.[1]

HAT complicated with liver failure is thought to be an indication for urgent retransplantation, and as for LDLT recipients, waiting for another graft can be difficult. That is why timely revascularization plays an important role. With the help of intra-operative and post-operative DUS, the success rate of immediate thrombectomy and reanastomosis is reported to be 50% to 67%. In this study, two patients with eHAT accepted an immediate thrombectomy and reanastomosis after the diagnosis was confirmed and satisfactory hepatic arterial blood flow was obtained with neither late vascular complications nor any sign of biliary complications up to the latest follow-up day. Endovascular thrombolysis is not commonly used because there is a significant risk of bleeding in the early post-operative period[1] and may cause arterial intima damage.

The routine immunosuppressive protocol was a basic double-drug therapy with steroids and calcineurin inhibitors (CNIs; tacrolimus was most commonly used, and cyclosporine as an alternative). CNIs were used at 36 h post-operatively, and plasma concentration of the drugs was monitored. Methylprednisolone was used during immune induction, and the dose was reduced and continued as maintenance therapy. As for patients aged 3 years or patients who accepted cross-blood group transplantation, mycophenolate mofetil was added to the immunosuppressive protocol. Basiliximab was regularly used in the patients with a bodyweight >25 kg intra-operatively and day 4 post-operatively.

The importance of systematic anticoagulant therapy has been emphasized in recent years. Our routine anticoagulant protocol was the early use of intravenous heparin ($10\ IU{\cdot}kg^{-1}{\cdot}h^{-1}$) and sequential oral warfarin. Based on our experience, oral warfarin therapy may be weaned sooner than 3 months for patients with better conditions of the hepatic artery, given that when discharged from the

hospital, oral warfarin therapy without proper supervision can be dangerous and hard to manage.

Intra-operative and post-operative DUS was the major method to assess hepatic arterial blood flow worldwide because it is simple, practical, and non-invasive. Although digital subtraction angiography remains the gold standard for diagnosing HAT,[9] the technique is sophisticated and needs anesthesia for pediatric patients. As for HAT developed in the early post-operative period, an invasive operation can be risky. The median time of eHAT diagnosis in this study was at post-operative day 5, Bekker *et al*[3] reported a median time of 6.9 days, and Kaneko *et al*[9] reported 6.2 days. So, we recommend DUS no fewer than two times a day in the first post-operative week. The frequency can be reduced to once daily in the second week.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients' parent or guardians have given their consent for their images and other clinical information to be reported in the journal. The patients' parent or guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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