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ORIGINAL ARTICLE

Endovascular interventions for hepatic artery complications immediately after pediatric liver transplantation

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Summary

Hepatic artery complications after living donor liver transplantation (LDLT) can directly affect both graft and recipient outcomes. For this reason, early diagnosis and treatment are essential. In the past, relaparotomy was generally employed to treat them. Following recent advances in interventional radiology, favorable outcomes have been reported with endovascular treatment. However, there is ongoing discussion regarding the best and safe time for definitive endovascular interventions. We herein report a retrospective analysis for six children with early hepatic artery complication after pediatric LDLT who underwent endovascular treatment as primary therapy at our institution. We evaluate the usefulness of endovascular treatment for hepatic artery complication and its optimal timing. The mean patient age was 11.9 months and mean body weight at LDLT was 6.7 kg. The mean duration between the transplantation and first endovascular treatment was 5.3 days. Five of the six patients were technically successful treated by only endovascular treatment. Of these five patients, two developed biliary complications. Endovascular procedures were performed 10 times in six patients without any complications and nine of the 10 procedures were successful. By selecting optimal devices, our findings suggest that endovascular treatment can be feasible and safe in the earliest time period after pediatric LDLT.

Introduction

Early hepatic artery complications after living donor liver transplantation (LDLT), including hepatic artery thrombosis, stenosis, spasm, kinks, and aneurysms can directly affect both the graft and recipient outcomes. For this reason, early diagnosis and treatment are essential when dealing with these complications. Although the incidence of early hepatic artery complications has been reduced, the reported incidence remains at 1.7–16.3% [1–13], and is higher in children than in adults [9]. The outcome of early hepatic artery complications is poor if the diagnosis is delayed. Sheiner *et al.* reported that the one-year survival rate was 65% for cases in which the diagnosis of early hepatic artery complications was delayed [14]. Some investigators have reported the death rate to be higher in patients with early hepatic artery complications even when re-transplantation was performed [15]. There are currently two major therapeutic options for the treatment of these complications: endovascular interventions and re-laparotomy. The former include intra-arterial thrombolysis, percutaneous transluminal angioplasty (PTA), and stent placement. The latter include thrombectomy, re-anastomosis, and re-transplantation. In the past, re-laparotomy was generally employed to treat early hepatic artery complications [4,16,17]. Owing to recent advances in interventional radiology, favorable outcomes comparable with those of re-lapalotomy have been reported with endovascular treatment [10,18,19]. However, there is ongoing discussion regarding the best and safest time for definitive endovascular interventions. We herein report a retrospective analysis of six patients with early hepatic artery complications who underwent endovascular treatment as primary therapy at our institution. Although our series is small, we evaluated the usefulness of endovascular treatment for early hepatic artery complications and also tried to elucidate its optimal timing.

Patients and methods

During a 10-year period from May 2001 to January 2010, 170 children underwent LDLT at our institution. Fourteen patients (8.2%) were diagnosed with early hepatic artery complications that needed treatment within 2 weeks after LDLT. Our initial treatment strategy for early hepatic artery complications was re-laparotomy as the primary therapy. Since December 2004, in collaboration with radiologists, endovascular treatment has now become the first choice of treatment. Of the 14 patients, six patients (42.8%) who underwent endovascular treatment as primary therapy were retrospectively analysed in this study. The primary diagnoses of these six patients included biliary atresia in four, neonatal hemochromatosis in one and graft failure in one case.

In all cases, elective LDLT was carried out using a left lateral segment or S2 mono-segment graft and there were no cases of auxiliary partial orthotopic liver transplantation. Arterial reconstruction was performed in an end-to-end fashion by interrupted suturing using 8-0 or 9-0 Nylon under a microscope. Biliary reconstruction was carried out with a choledochojejunostomy. Primary abdominal closure could be performed in all patients and there were no signs of abdominal compartment syndrome in any cases.

During the postoperative period, anticoagulation therapy was started by using intravenous dalteparin sodium (100 U/kg/day). When the hepatic artery was considered to be stenotic, we increased the anticoagulation therapy [by increasing the dose of dalteparin sodium and/or adding the systemic administration of urokinase at a total dose of 90 000–180 000 units/day, adjusted with reference to the activated clotting time (target levels: 180–200 s) and/or the activated partial thromboplastin time (target levels: 50–70 s)].

Based on our institutional policy, Doppler ultrasonography was routinely performed, three times a day until postoperative day 3, twice a day until postoperative day 7, and once per day until the patients were discharged from the hospital. If abnormal serum liver function tests were observed, we did not hesitate to perform Doppler ultrasonography as soon as possible. With Doppler ultrasonography, we measured the peak systolic velocity and the resistive index (peak systolic velocity-end diastolic velocity/peak systolic velocity) just distal to the anastomotic site. The hepatic artery was considered to be stenotic when the peak systolic velocity was less than 20.0 cm/s and/or the resistive index was less than 0.6. Thereafter, abdominal angiography was carried out when the peak systolic velocity was less than 10.0 cm/s and the resistive index was less than 0.5. If Doppler ultrasonography revealed the progressive blood flow reduction through the hepatic artery, even if there were no signs of serum liver function tests worsening, abdominal angiography was carried out under general anesthesia for the purposes of diagnosis and treatment as described below.

A 4-French size sheath (Super sheath, 4 Fr, 10 cm; Medikit®, Tokyo, Japan) was placed through the femoral artery by cut-down or percutaneous ultrasonography guided puncture. A percutaneous ultrasonography guided puncture was carried out by radiologists and a cut-down was performed by surgeons. We performed celiac arteriography (case 6; superior mesenteric arteriography) with a 4-French size angio-catheter (Glidecath, 4 Fr, 70 cm; Cobra, Terumo®, Tokyo, Japan) and established a diagnosis of hepatic artery stenosis. If arteriography revealed a decrease or disappearance of blood flow through the anastomosed site, the first treatment was intra-arterial injection of isosorbide nitrate and/or urokinase (total dose 5000–20 000 units, adjusted according to the findings). Only during the arteriography was the intra-arterial infusion of urokinase performed. Prior to beginning endovascular intervention, the patients received 5000 units of heparin. When stenosis was noted at the anastomosed site by arteriography afterwards (the luminal diameter of the hepatic artery decreased by more than 50%), we performed vasodilation with a PTA balloon catheter. A micro-guidewire (Silverspeed-10, 0.010 inch, 200 cm; EV3®, Irvine, CA, USA) was first advanced into the graft left hepatic artery and then a microcatheter (Microferret-18, 2.4 Fr, 130 cm; COOK®, Bloomington, IN, USA) was inserted along the micro-guidewire into the intrahepatic artery. The micro-guidewire was advanced, followed by the insertion of a balloon catheter. PTA was then performed with a percutaneous transluminal coronary angioplasty balloon catheter. Until 2007, Ryujin Plus (2.4 Fr, 145 cm, semicompliant balloon; Terumo®, Tokyo, Japan) was selected for use as the balloon catheter. Since 2007, IKAZUCHI-X (2.1 Fr, 130 cm, semicompliant balloon; Kaneka®, Osaka, Japan), capable of passing through the lumen of the guide catheter (an angio-catheter), has been used. The balloon size was selected based on the diameter of the hepatic artery distal to the stenosis. After PTA, if the artery remained stenotic, we placed a stent (MULTI-LINK MINI VISION stent, bare metal, balloon expandable type; Abbott®, Abbott Park, IL, USA) in the anastomosed site. The stent size was selected, based on the diameter of the graft hepatic artery. If kinking of the anastomotic site was thought to be the cause of the reduced blood flow, we similarly decided to place a stent in the anastomosed site. Following stent placement, antiplatelet (acetylsalicylic acid, 2 mg/kg/day) medication was administered to prevent thrombosis for at least 3 months. The success of endovascular interventions was defined when the peak systolic velocity was more than 20.0 cm/s and/or the resistive index was more than 0.6. Based on our institutional policy, if endovascular treatment was not possible or efficacious, and then we did not hesitate to convert the procedure into a re-laparotomy. Our current institutional treatment scheme in the early time period after LT is shown in Fig. 1.

At our institution, the imaging surveillance methods used for follow-up were Doppler ultrasonography and contrast enhanced computed tomography. Doppler ultrasonography was performed routinely at 1, 3, 5, and 9 months and then every 6 months after liver transplant (LT). Contrast enhanced computed tomography was performed routinely at 2, 6, and 12 months and then every 12 months after LT.

Results

Their postoperative follow-up period ranged from 8 to 68 months. The patient age ranged from 13 days to 3 years 1 month (mean: 11.9 months) and body weight at LDLT ranged from 2.6 to 11.1 kg (mean: 6.7 kg) (Table 1). The neonatal patient (case 4) has been described elsewhere [20]. The artery of the recipient anastomosed site included the right hepatic artery in three, left hepatic artery in two, and jejunal artery of the Roux-en-Y limb in one case. In case 1, an interposition graft from the donor right gastroepiploic artery was used to secure a sufficient length for the reconstruction. In case 6, an adequate artery for reconstruction was lacking at re-transplantation. We reconstructed the artery by using the jejunal artery of the Roux-en-Y limb, as we judged it to be the most appropriate alternative. The artery of the graft anastomosed site was the left hepatic artery in all cases. The mean diameter of the recipient artery was 1.8 mm (range: 1.0–2.5 mm) and the graft artery was 2.2 mm (range: 1.8–2.5 mm). The mean duration between the transplantation and first endovascular treatment was 5.3 days (range: 3–8 days) (Table 2). The first endovascular treatment included PTA in five patients and intra-arterial thrombolysis in one patient. Recurrent stenosis of the hepatic artery occurred in three of the five patients who underwent PTA (60%). Two of these three patients were successfully treated with repeated PTA without complications, but case 6 required stent (2.5–18 mm) placement because hepatic blood flow had been reduced because of kinking of the anastomosed site (Fig. 2). In one of the three patients (case 1), restenosis occurred, after which a third PTA was performed without any complications. In case 2, we had to convert from intra-arterial thrombolysis to open thrombectomy because the guidewire was not passed through the anastomosed site. All six patients survived for more than 8 months after the hepatic artery complication without graft loss. Biliary complications such as intra-hepatic strictures because of the decreased arterial blood flow occurred in two of six patients (33.3%). As a consequence, five of the six patients (83.3%) were technically successful treated by

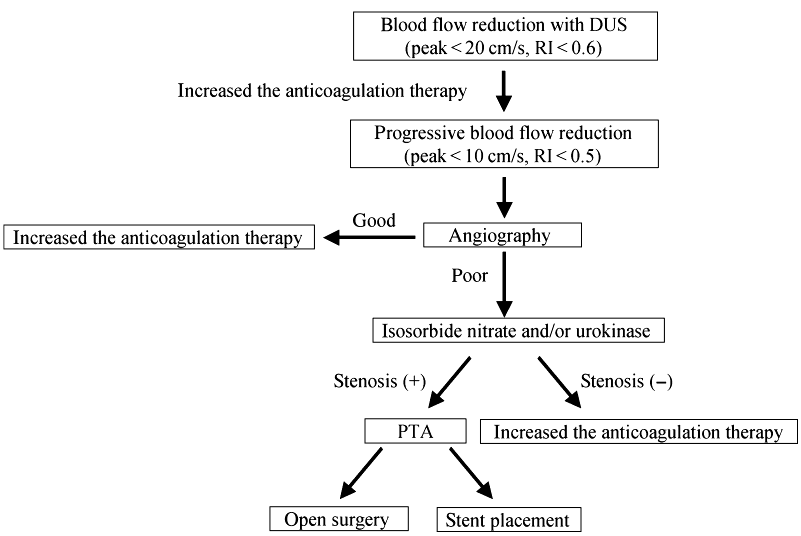

Figure 1 Treatment scheme in the early time period after LT. DUS, Doppler ultrasonography; PTA, percutaneous transluminal angioplasty; LT, liver transplantation.

Table 1. Characteristics of the six recipients.

Case	Gender	Indication	Age at LT	BW at LT (kg)	ABO-blood type matching	Graft type (segment)	Graft volume (g)	% SLV	Recipient artery (diameter) (mm)	Graft artery (diameter) (mm)	Interposition graft
1	F	BA	10 months	6.5	identical	II and III	226	95.8	RHA (1.0)	LHA (2.3)	RGEA
2	F	BA	9 months	7.5	identical	II and III	204	78.5	LHA (2.0)	LHA (1.8)	No
3	F	BA	8 months	5.8	identical	II and III	172	79.3	LHA (2.0)	LHA (2.0)	No
4	F	NH	13 days	2.6	compatible	reduced II	98	75.4	RHA (1.5)	LHA (2.5)	No
5	M	BA	7 months	6.7	identical	II and III	224	96.6	RHA (2.5)	LHA (2.0)	No
6	F	graft failure	3 years 1 month	11.1	identical	II and III	260	70.8	JA (1.5)	LHA (2.5)	No
Average			11.9 months	6.7			197.3	82.7	1.8	2.2	

LT, liver transplantation; BW, body weight; SLV, standard liver volume; BA, biliary atresia; NH, neonatal hemochromatosis; LHA, 1eft hepatic artery; RHA, right hepatic artery; RGEA, right gastro epiproic artery; JA, jejunal artery.

Table 2. Summary of treatment and outcome of patients with hepatic artery complications.

Case	Postoperative day of EVIs	Access to the FA	Type of complication	Treatment	Operation time (min)	Fluoroscopy time	Result	Survival outcome
1	4	Puncture	Stenosis	PTA	133	NA	Recurrence	
	7	Puncture	Stenosis	PTA	138	NA	Recurrence	
	16	Puncture	Stenosis	PTA	384	NA	Biliary stenosis	68m, alive
2	6	Puncture	Almost obstruction	Thrombolysis	205	NA	Failure	
	7	–	Thrombosis	Open thrombectomy	389	–	Success	41m, alive
3	8	Puncture	Stenosis	PTA	314	92 min	Biliary stenosis	13m, alive
4	3	Cut down	Stenosis	PTA	123	14 min	Recurrence	
	27	Cut down	Stenosis	PTA	300	29 min	Success	13m, alive
5	3	Puncture	Stenosis	PTA	69	15 min	Success	9m, alive
6	8	Puncture	Kinking	PTA	117	40 min	Recurrence	
	8	*	Kinking	PTA + stenting	325	95 min	Success	8m, alive

EVIs, endovascular interventions; FA, femoral artery; PTA, percutaneous transluminal angioplasty; NA, not available.
*The angio-sheath was left in place and used.

only endovascular treatment. Of the five successfully treated patients, two developed biliary complications, so the clinical success was three out of five successfully treated patients (60%). Endovascular procedures were performed 10 times in six patients without any complications and nine of the 10 procedures (90.0%) were successful.

Discussion

The incidence of early hepatic artery complications following LDLT is reportedly 4.2–16.3% [10–13] and 1.7–10.0% for children [1–5,8]. Treatments are roughly divided into endovascular treatment and re-laparotomy, with the latter including thrombectomy, re-anastomosis, and re-transplantation. In the past, re-laparotomy was generally employed to treat early hepatic artery complications [4,16,17], but the incidence of relapse is as high as 12% [16]. Even when hepatic artery complications are diagnosed at early stages and re-anastomosis is performed with laparotomy, the graft may be severely damaged by temporary complete obstruction of arterial blood flow at the vascular anastomosis. Furthermore, when re-anastomosis and/or re-transplantation become necessary, arterial reconstruction can be extremely difficult because of severe inflammation around the hepatic artery and the lack of an adequate artery for reconstruction. Frequently, we found that the native recipient hepatic artery was not in good condition, such that an alternative method was required. In most cases, re-anastomosis is more difficult than primary hepatic artery reconstruction.

Endovascular intervention including intra-arterial thrombolysis, PTA, and stent placement, is less invasive, but there has been uncertainty with regard to the risk of complications and the efficacy of these procedures. For these reasons, endovascular treatment has not been adopted as the first-line treatment for early hepatic artery complications. However, recent technical improvements have made it possible to perform endovascular interventions

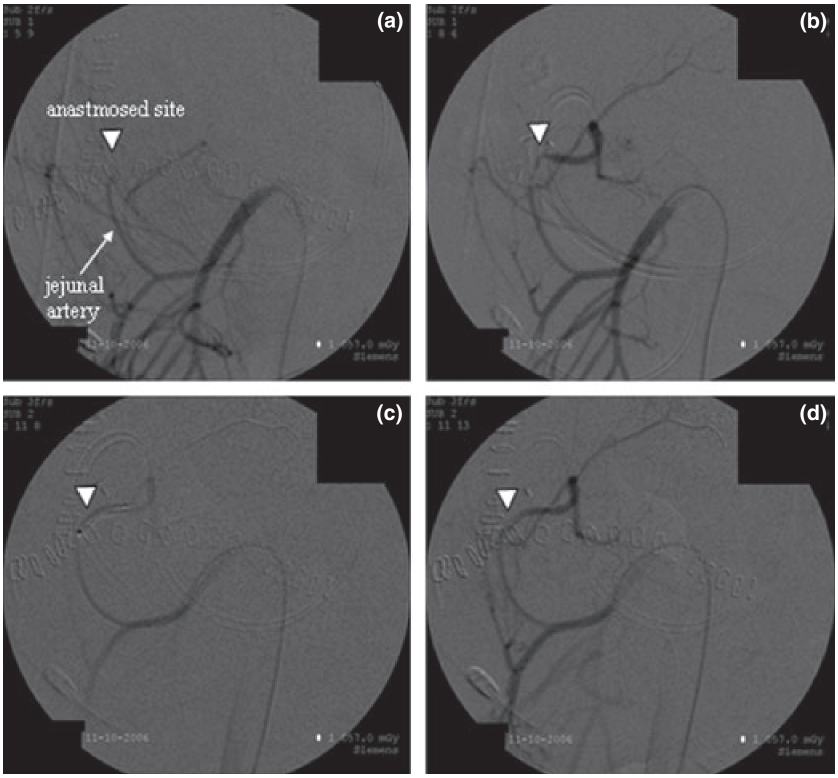

Figure 2 Endovascular treatment for hepatic arterial anastomosis in case 6. (a) Superior mesenteric arteriography failed to allow visualization of intrahepatic artery. (b) After balloon PTA, superior mesenteric arteriography showed improvement of the blood flow. However, the anastomosed site remained kinked. (c) Stent was deployed and the kinking of the anastomosed site resolved. (d) After stent deployment, favorable steady blood flow was achieved. PTA, percutaneous transluminal angioplasty.

on small children with improved safety. Favorable outcomes of endovascular treatment as a means of treating these complications have been reported [6,10,18,19,21]. Endovascular interventions can easily be selected for diagnostic purposes and, if decreased blood flow through the hepatic artery is detected, treatment can be started immediately. Therefore, these types of intervention are reasonable methods allowing for both early detection and early treatment. Furthermore, they are superior to re-laparotomy because the time until arterial blood supply to the graft improves can be shorter. The success rate with endovascular treatment is reportedly 81.0–94.4% [6,10,18] and successful endovascular treatment in children has also been reported [10,22]. Complications possibly arising after endovascular treatment include arterial dissection, perforation and so on, with the incidence reportedly being 5.0–10.0% [6,10,18]. In our series, all of the cases were pediatric patients, and five of the six patients (83.3%) were treated successfully using only endovascular interventions. Of the five successfully treated patients, two developed biliary complications and so the clinical success rate was three out of five successfully treated patients (60%). Endovascular procedures were performed 10 times without complications in these six patients and nine of the 10 procedures (90.0%) were successful. In our present case 2, the same guidewire used in the other cases could not be passed through the anastomosed site. We could not perform PTA, and therefore had to convert the procedure to an open thrombectomy. We thus confirmed that there were no endovascular complications, such as a dissection, at the subsequent open thrombectomy. Great care is required not to overdiagnose and overtreat such cases. On the other hand, if the blood flow is completely obstructed by thrombosis, then the guidewire cannot be passed through the anastomosed site and then endovascular intervention becomes impossible. It is necessary to avoid any delay in making the diagnosis and starting treatment. We therefore repeatedly perform Doppler ultrasonography and confirm that no progressive blood flow reduction has occurred.

In children, the devices that can be used for endovascular intervention are limited because their arteries are small. In our study, all patients were treated using a 4 French sheath and angio-catheter. As a result, the selection of the balloon catheter was also restricted. Although the applicable devices for children are restricted, safe treatment with endovascular techniques seems possible in neonates, as in adults, if an optimal device tailored to the vascular diameter can be selected.

However, further investigations are needed to solve the high recurrence rate of endovascular treatment, such as was necessary in three of our patients and following four of the nine procedures (44.4%). Intra-arterial thrombolysis and PTA can result in restoration of the flow without resolving the underlying anatomical defects, including kinks, anastomotic stenosis and stricture, which can lead to relapse, and often requires stent placement. For stent treatment of hepatic artery complications after liver transplantation, favorable outcomes have been reported in both adults and infants [23–25]. In our present case 6, stent treatment was carried out because kinking of the anastomosed site reduced hepatic blood flow and favorable steady blood flow was achieved after the stent placement. However, as no series has documented the long-term patency of stent placement and the relationship between growth of the child and stent treatment for hepatic artery complications after pediatric liver transplantation, we must follow this patient closely and over long-term.

Endovascular intervention enables us to diagnose and simultaneously treat such complications in a less invasive and more useful manner that facilitates the early detection and treatment of hepatic artery complications. It is thus promising as a first choice of treatment for early hepatic artery complications. Although some reports have suggested an optimal timing for endovascular interventions after liver transplantation (7 days to 3 weeks) [10,23], there is currently no consensus about the timing. In the earliest time period after transplantation, endovascular treatment was considered to have a potentially high risk for complications including dissection, thrombosis, distal embolism, rupture, and pseudoaneurysm; however, there is currently no evidence for what time period is safe. In addition, in a lot of the past reports, complications of endovascular treatment have occurred when they were found not only during the early period after transplantation, but even several weeks later. It is difficult to determine the optimal interval between surgical reconstruction that will secure the safety of endovascular treatment. In our institutional policy, we select the optimal device, and to avoid excessive stress on the anastomosed site, used the above (relatively short) time period after transplantation. Because of these features, we make it a rule to carry out endovascular treatment as the first-line therapy for early hepatic artery complications even in the earliest time period after transplantation. In our results, the mean duration between the transplantation and first endovascular procedure was 5.3 days. Although the earliest case occurred 3 days after transplantation, a favorable outcome was obtained without any complications. Successful PTA of subacute to chronic strictures is presumed to result from the disruption of anastomotic intimal hyperplasia/fibrosis or the release of an overly tight suture line. The pathophysiological mechanism responsible for the stenotic changes immediately after surgery are thought to be spasm, clamp injury, thrombosis and/or a combination of these factors. It is difficult to distinguish between these differences. Therefore, for the treatment of these factors, we believe that an endovascular approach is more reasonable than extravascular approaches, such as re-anastomosis. Although our series is small, our results suggest that endovascular treatment is a feasible and safe option for the treatment of complications, even in the earliest time period after transplantation. It is therefore desirable that more objective and concrete guidelines be developed in the future for the treatment of early hepatic artery complications. For that purpose, further investigations will need to be conducted worldwide.

Conclusion

We recently succeeded in safely using endovascular treatment for infants with early hepatic artery complications after LDLT and obtained a favorable outcome. Although endovascular treatment needs to be examined in further studies to reduce the rate of relapse, it is a reasonable method that allows for both early detection and early treatment. By selecting the optimal device and avoiding excessive stress to the anastomosed site, we believe that endovascular treatment can be a feasible and safe option for the treatment of hepatic artery complications, even in the earliest time period after transplantation.

Authorship

TW: study organization and paper writing. YS, KM, MU, TU, SE, SH and MN: study performing. KH, YY and HK: supervisors.

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