Intensive Doppler Ultrasonography for Early Detection of Hepatic Artery Thrombosis After Adult Living Donor Liver Transplantation

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Source of support: Departmental sources

Background: Early hepatic artery thrombosis (eHAT) is a severe arterial complication leading to biliary complications and graft failure in living donor liver transplantation (LDLT). This study sought to early identify the abnormal waveforms of eHAT by using intensive Doppler ultrasonography (DUS) after LDLT and to assess the clinical outcome in these eHAT patients.

Material/Methods: DUS for 419 adult LDLT recipients was performed twice after vascular anastomosis during liver transplantation and once a day at the bedside for at least 2 weeks.

Results: Nine adult LDLT recipients with eHAT were identified by using bedside DUS with subsequent computed tomography angiography (CTA). All eHAT cases were noted in the first 2 weeks. Five patients with CTA findings of partial thrombus with the small visualized intrahepatic hepatic artery (HA) were treated with intravenous thrombolysis (IVT) (medical group). Another 4 patients with CTA findings of extrahepatic HA occlusion and nonvisualization of intrahepatic HAs were treated by arterial re-anastomosis (surgical group). The prevalence of long-term non-anastomotic biliary strictures was 33.3% in the surgical group. Intensive post-LDLT DUS is a convenient and sensitive tool for eHAT detection.

Conclusions: Subsequent CTA gives valid information on occluded arteries and associated findings, which impact decision-making and are correlated with patient outcome. Our protocol of DUS has high sensitivity and diagnostic accuracy for use in eHAT patients with partial occlusion, and it can be applied for IVT treatment, avoiding the need for reoperation and preventing long-term biliary complications.

MeSH Keywords: Arterial Occlusive Diseases • Liver Transplantation • Thrombolytic Therapy • Ultrasonography, Doppler, Color

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/924336

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]
Background

Early hepatic artery thrombosis (eHAT) is a severe arterial complication in living donor liver transplantation (LDLT). eHAT can lead to biliary complications, graft loss, and mortality. In a previous review study [1], the median incidence of eHAT was 4.4%, with a range from 0% to 20%. eHAT is a major cause of graft loss (53.1%) and mortality (33.3%) in the early postoperative period. Early revascularization (including medical thrombolysis, and surgical thrombectomy with or without revision of anastomosis) and retransplantation are viable options for saving grafts and lives. Even without graft loss, biliary complications such as biliary ischemia, necrosis, bilomas, and non-anastomotic biliary strictures can occur in recipients, especially those with inadequate hepatic arterial flow [2]. Different treatment modalities may be chosen according to patient clinical condition and image findings. Therefore, early diagnosis of eHAT can enable treatment as soon as possible to avoid mortality and long-term biliary complications.

Doppler ultrasonography (DUS) is the established method for initial screening of vascular abnormalities after LDLT. The portability of DUS and its high sensitivity and specificity for detecting eHAT make it ideal for evaluation of LDLT recipients [3]. Early detection of eHAT by DUS before clinical presentation allowing early management leads to lower incidence of biliary complications and better patient survival [4]. However, highly variable DUS screening protocols for eHAT with respect to frequency and interval of screening and the time period after operation are reported [1]. In the detection of eHAT, Doppler waveforms of the postanastomotic hepatic artery (HA) are established indicators. The DUS criteria for eHAT include no Doppler signal or tardus parvus waveforms (with resistive index [RI] <0.5 and systolic acceleration time >0.08 s) [2,5] or peak systolic velocity (PSV) less than or equal to 48 cm/s [6]. False-positive cases may be seen in the presence of vascular kinks and anastomotic site edema. Stenosis of the recipient celiac axis can also cause decreased hepatic arterial resistive indices in the transplanted liver. Correction of the Doppler angle can help in differential diagnosis [7].

Owing to the false-positive results of DUS, eHAT cannot be diagnosed by DUS only [6,8]. In the case of suspicious or inclusive DUS, computed tomography angiography (CTA) is useful to confirm eHAT. CTA gives a rapid, accurate depiction of hepatic arterial anatomy after LDLT [8]. Many previous studies demonstrated the correlation between DUS and CTA findings [6,8] but fewer publications have discussed the relationship with image findings, treatment choice, and clinical outcome. To the best of our knowledge, there is no previous publication assessing imaging criteria of CTA for use in selecting treatment options in eHAT patients. A summary of CTA imaging criteria that correlates with the prognosis after medication or surgery in eHAT patients may help in selecting treatments.

The present study sought to perform early identification of abnormal waveforms of HAT by using DUS after LDLT, to set up the imaging criteria of CTA for assessing treatment options in eHAT patients, and to assess the effect and prognosis with long-term non-anastomotic biliary complications in HAT patients treated with medication or surgery.

Material and Methods

This was a retrospective single-center study in Taiwan performed from January 2013 to September 2016. All hepatic artery reconstructions were performed by a single microvascular surgeon under an operating microscope with 6–15× magnification. All intraoperative and postoperative DUS were performed by specialized radiologists. The post-LDLT arterial evaluation included DUS and CTA imaging. For all LDLT recipients, intraoperative DUS was performed twice in the surgical room (once after artery anastomosis and again after surgical wound closure), and immediate re-do anastomosis was done in all of those patients with intraoperative hepatic artery thrombosis or intimal dissections, who did well in the follow-up DUS at the end of the operation. Intensive post-LDLT bedside DUS was performed once a day by specialized radiologists for at least 2 weeks, every other day in the third week, and twice a week after that until discharge. DUS was performed using an Acuson scanner (Acuson, Mountain View, CA, USA) with a 4.0- or 7.0-MHz transducer available for color Doppler imaging in all recipients to measure the DUS waveform, PSV, and RI, with proper angle correction in the postanastomotic HA along the hepatic hilum. For those patients with suspicious postoperative eHAT, subsequent CTA was then performed to demonstrate the presence of contrast medium filling in postanastomotic and intrahepatic arteries, and further detailed information on the liver graft. CTA studies were conducted using a multislice CT, Somatom Volume Zone scanner (Siemens AG, Erlangen, Germany). Detailed 3-dimensional images of the celiac and superior mesenteric arteries were obtained for thorough assessment using multiple-plane reconstruction and oblique coronal maximum-intensity projection with slab thickness of 3 mm. Tacrolimus-based immunosuppression was employed for adult recipients since post-LDLT day 1, keeping the trough level at 5–8 ng/ml. Anticoagulation therapy was administered immediately after the surgery. The protocol of postoperative anticoagulation was heparin continuous infusion started from 50 IU/kg/day, maintaining APTT 1.5–2 times for 2 weeks. All postoperative eHAT patients were treated with intravenous thrombolysis (IVT) continuing the postoperative heparin infusion only (n=5, medical group) or surgical revascularization plus heparin infusion (n=4, surgical group). After the patients...
were discharged, DUS imaging was also performed for long-term follow-up of vascular or biliary complications. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 22, SPSS, Inc., Chicago, IL, USA). The group differences of clinical data were compared by the independent-samples t test. The group differences in mortality and morbidity were compared using the Pearson chi-square test. Statistical significance was set at P<0.05. The Institutional Review Board approved this study, and each participant's private information was protected.

Results

The demographic, imaging, and clinical parameters are shown in Table 1. Nine adult LDLT recipients with postoperative eHAT were identified from 419 LDLT recipients by bedside DUS with subsequent CTA between January 2013 and September 2016. There were 7 male and 2 female recipients with abnormal Doppler flows, with a mean age of 55.3±9.70 years (range, 38–66 years). All grafts were procured from adult living donors. The grafts consisted of 1 extended left lateral segment (segments 2, 3, and 4) and 4 left and 4 right lobes. The mean liver graft weight was 582.8±134.2 g (range, 396–830 g). The liver enzymes and bilirubin were evaluated and found not to be significantly associated with the image findings or treatment choice.

DUS findings

All adult LDLT recipients received intensive post-LDLT bedside DUS for at least 2 weeks. Figure 1A demonstrates a normal arterial curve at the pre-anastomotic artery. All abnormal Doppler flows were noted in the first 2 weeks, ranging from 1 to 14 days (mean 8.6±4.8 days). Using DUS, the incidence of abnormal Doppler arterial flow in the LDLT recipients was 9/419 (2.1%). The abnormal Doppler flows included: (1) tardus parvus waveform (n=5; Figure 1B), which presents as prolonged systolic acceleration and small systolic amplitude; and (2) complete absence of arterial wave (n=4). The mean PSV was 24.6±10.66 (cm/second), and the mean RI was 0.52±0.08 in recipients with tardus parvus waveform.

CTA findings

eHAT was diagnosed using CTA imaging as the criterion standard. All of the 9 adult recipients with abnormal Doppler arterial flow had subsequent CTA imaging. Eight eHAT patients were confirmed using CTA images. In CTA findings of eHAT, there were 2 abnormal patterns of intrahepatic arterial flow. Partial occlusion of HAs (n=5; Figure 1C) showed single or multifocal filling defect at pre- and/or postanastomotic HAs with small caliber of intrahepatic arterial contrast filling (Figure 1D is the supplementary image of the same patient in Figure 1A–1C). Total occlusion of HAs (n=3; Figure 2A) showed disruption of HA and non-opacification of intrahepatic arterial branches (Figure 2B–2D are the supplementary images of the same patient in Figure 2A). Other complications, such as infarct or hematoma, can also be noted in CTA imaging. Of the 9 adult recipients with abnormal Doppler arterial flow, 8 were diagnosed with eHAT by CTA findings. One case of false-positive eHAT with Doppler tardus parvus waveform (Figure 3A) but patency of HAs in CTA imaging (Figure 3B) had smooth contour of the contrast material-filled artery without any filling defect or luminal disruption in both pre- and postanastomotic segments (Figure 3C, 3D are the supplementary images of the same patient of Figure 3A, 3B). The incidence of eHAT in the LDLT recipients was 9/419 (2.1%). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and false-positive rate of the intensive post-LDLT bedside DUS were 100%, 99.5%, 88.9%, 100%, 99.5%, and 0.5%, respectively.

Treatment choice, prognosis, and long-term complications

According to the CTA findings and clinical conditions, the eHAT patients were treated by IVT (n=5, medical group), or surgical revascularization (n=4, surgical group). All of the 4 patients with surgical revascularization had surgical findings of HAT. The rate of reoperation for eHAT in all adult LDLT patients was 1.0% in this study. The imaging findings, clinical condition, and outcomes of these adult LDLT recipients with different treatment choices are demonstrated in Table 1. Of the 5 patients who received medical thrombolysis, all had graft salvage, but 1 (20%) had persistent occlusion of right posterior HA with both right anterior and posterior HA anastomosis. Follow-up DUS revealed improved Doppler arterial blood flow after 1 to 2 days in the medical group. Of the 4 who received surgical thrombolysis, 1 received a second transplant and 1 died. The patient who died had a partial arterial occlusion and subphrenic hematoma noted in CTA on postoperative day 12. The routine postoperative anticoagulation was held temporarily. Due to eHAT and internal bleeding, thrombectomy and re-anastomosis of the donor hepatic artery to recipient gastroepiploic artery were done. After 2 re-anastomoses and 56 days of ICU care, this patient died from internal bleeding and multiple organ failure. The mortality rate was 1/4 (25%) in the surgical group and 0 in the medical group (P=0.236). Long-term non-anastomotic biliary strictures were noted in one-third (33.3%) of patients in the surgical group and 0 in the medical group. The incidence of non-anastomotic biliary complication in all eHAT patients was 12.5%.
Table 1. The demographic and clinical characteristics of adult LDLT recipients with abnormal Doppler flows in different treatment groups.

<table>
<thead>
<tr>
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<th>Medical group (n=5)</th>
<th>Surgical group (n=4)</th>
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<tr>
<td></td>
<td>n</td>
<td>Mean±SD</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>5</td>
<td>55.6±11.1</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>55.0±11.1</td>
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<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>Serum AST (U/L)</td>
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<tr>
<td>Serum ALT (U/L)</td>
<td></td>
<td>137.20±64.61</td>
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<tr>
<td>Serum TB (mg/dL)</td>
<td></td>
<td>1.56±0.72</td>
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<tr>
<td>Serum DB (mg/dL)</td>
<td></td>
<td>0.61±0.42</td>
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<td>Post-LDLT Doppler US of HA</td>
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<td>Doppler US waveform</td>
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<tr>
<td>Tardus parvus</td>
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<td>0.49±0.08</td>
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<tr>
<td>CTA of intrahepatic HA</td>
<td></td>
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<tr>
<td>Patency</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial occlusion</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Time of discharge (POD)</td>
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<td>51.2±10.5</td>
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<td>Long-term follow-up</td>
<td></td>
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<tr>
<td>Mortality *</td>
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<td>1</td>
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<tr>
<td>Biliary dilatation</td>
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<td>1</td>
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<tr>
<td>Serum TB (mg/dL)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Serum DB (mg/dL)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Serum TB (mg/dL)</td>
<td>0.56±0.23</td>
<td>0.3–0.8</td>
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<tr>
<td>Serum DB (mg/dL)</td>
<td>0.14±0.05</td>
<td>0.1–0.2</td>
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</table>

* Mortality case due to internal bleeding and multiorgan failure. ALT – alanine transaminase; AST – aspartate transaminase; DB – direct bilirubin; HA – hepatic artery; HAT – hepatic artery thrombosis; LDLT – living donor liver transplantation; N/A – not applicable; POD – postoperative day; PSV – peak systolic velocity; RI – resistive index; TB – total bilirubin; US – ultrasonography.
Discussion

In a previous systematic review that included 71 studies, the median incidence of eHAT in liver transplants was 4.4% (range, 0–20.2%, mean 3.9%), with the separated incidence 6.9% versus 3.8% in the study period between 1982 and 1996 versus between 1993 and 2006 [1]. In previous data from our hospital, 3/126 (2.4%) LDLT patients had reoperation for HAT between 1999 and 2006 [9]. Under our intensive DUS protocol, immediate intraoperative re-do anastomosis could be done and postoperative eHAT can be detected early. We excluded these intraoperative HAT or intimal dissection events and only considered postoperative eHAT. In the present study, the incidence of eHAT was 2.1% and the rate of reoperation for eHAT was 1.0%. All thromboses occurred within 2 weeks after LDLT and could be detected using bedside DUS. The patients with abnormal Doppler waveforms underwent CTA study for further image information and received either medical or surgical treatment. The incidence of long-term non-anastomotic biliary complications in eHAT patient was 12.5%, which is much lower than the incidence (45.2%) reported in a previous study [10].

The importance of eHAT is based on the fact that the intrahepatic biliary epithelium is perfused solely by the HA [11]. eHAT is a significant risk factor for biliary complications [12], non-anastomotic biliary stricture [13], and even graft loss [1]. Timely diagnosis and treatment of eHAT are of extreme importance for graft and patient survival. We found a 12.5% incidence of long-term non-anastomotic biliary dilatation in all eHAT patients. Graft salvage and 1-year survival in all eHAT

Figure 1. The 66-year-old male hepatocellular carcinoma patient received LDLT with right lobe graft. Right hepatic artery of the graft were anastomosed with the recipient’s right hepatic artery. An abnormal Doppler waveform was detected on post-LDLT day 12. (A) Doppler US demonstrated normal arterial curve at the pre-anastomotic artery (white arrowhead), and (B) tardus parvus waveform at post-anastomotic intrahepatic artery (RI=0.46, PSV=10.1 cm/s, white arrow). (C) Subsequent CTA on the same day demonstrated multifocal disruption of post-anastomotic artery (black arrowheads) and faint opacification of intrahepatic arterial filling (black arrows), suggesting partial occlusion. After IVT, (D) DUS on the next day demonstrated recovered arterial curve (RI=0.64, PSV=47 cm/s).

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Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

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patients undergoing revascularization were 87.5% and 87.5%, respectively, in our study, whereas previous studies reported incidences of biliary complications from 45.2% to 77.8% in patients with HAT [10,14]. In Sheiner’s study, the overall graft salvage and 1-year survival were 40.6% and 75%, respectively, in eHAT patients [4]. The better prognosis in our hospital may partially be due to use of intensive DUS for early detection of thrombus formation in the early stage. Early detection of eHAT can lead to early revascularization and prevent further progression to complete arterial occlusion, hepatic infarct, and biliary complications. DUS is a recognized method for initial screening of vascular abnormalities after LDLT, but it cannot identify thrombosis, stricture, or other processes causing slow arterial flow or obstruction. Although CTA is not the criterion standard for HAT diagnosis, it is one of the most accurate imaging indicators of HAT, in addition to diagnostic angiography. The screening protocols for eHAT are variable with respect to frequency and interval of screening and the time period in different studies and hospitals [1]. Based on our experience and the data in this study, eHAT almost always occurs within 2 weeks after transplantation. Intensive DUS once a day for at least 2 weeks is an appropriate protocol for early detection of eHAT. Tardus parvus waveform or absent arterial wave in DUS is very sensitive (100%) and has an acceptable PPV (88.9%) for eHAT. False-positive diagnosis of HAT has been reported to be more common during the early postoperative period, possibly because of surgical edema, with the tardus parvus waveform occasionally returning to normal within a few days [6]. We also found 1 case of false-positive diagnosis of eHAT with tardus parvus waveform (RI=0.58 and
A 59-year-old male liver cirrhosis patient received LDLT with left lobe graft. Left hepatic artery of the graft was anastomosed with the recipient’s right hepatic artery. (A) Compared with the previous day, the Doppler US demonstrated declined arterial flow with prolonged systolic acceleration and small systolic amplitude on post-LDLT day 3. (B) Subsequent CTA on the same day demonstrated patency of LHA (white arrow) without any arterial filling defect or infarcted liver parenchyma. (C) Doppler US in following days demonstrated patency of LHA with relative normal arterial curve and resistance index=0.67. (D) Follow-up CTA 9 month later demonstrated regeneration of graft liver, patency of LHA, and no biliary dilatation.

PSV=37 cm/s) noted on post-LDLT day 3 (Figure 3). Subsequent CTA on the same day demonstrated patency of the LHA without any arterial filling defect or infarcted liver parenchyma. DUS of the same patient on the next day demonstrated patency of the anastomotic HA with normal arterial curve (RI=0.67 and PSV=53.5 cm/s). Although there may be some false-positive diagnoses of eHAT by DUS, intensive DUS is still a good tool for use in early detection before clinical symptoms or laboratory data change. Intensive screening protocols once per day for 2 weeks after LDLT provide the chance for early detection and treatment and decreasing the incidence of biliary complication in eHAT patients.

Diagnostic confirmation by CTA is useful to detect the presence of eHAT and also to show more information on vascularization, including the length and site of the thrombus, flow of intrahepatic collateral arteries, location of anastomotic artery, alternative arteries for possible reconstruction in case of injury of recipient-side HA, and other complications such as hepatic infarct, hematoma, and portal vein or IVC thrombus, which play important roles in selecting the therapeutic strategy [15]. These image findings may or may not alter the treatment options for reoperation. Based on our experience and retrospective results in this study, a higher proportion of surgical revascularization in those patients with total occlusion of extrahepatic HA and nonvisualization of intrahepatic HAs and/or other complications was noted by CTA (Figure 2). In those patients with partial arterial occlusion and with small visualized intrahepatic HA or even patency HA in CTA studies (Figure 1), medical revascularization has a good success rate (80%) without any
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long-term biliary complications. The complete loss of arterial flow in the early postoperative period in the surgical group induces more biliary complications compared to the weak arterial flow in the medical group [16]. It is reasonable that the patients with a higher degree of eHAT have more complicated abnormalities in CTA and more long-term biliary complications. DUS has high diagnostic accuracy for early identification of partial occlusion in eHAT patients, leads to higher potential of medical thrombolysis, and avoids reoperation, but surgical intervention should be still considered in patients with higher degrees of eHAT, in which medical thrombolysis alone may not be successful.

Although we only reported IVT and reoperation as the treatment of eHAT in this study, there are still other options, such as transcatheter intra-arterial thrombolysis (IAT), percutaneous transluminal angioplasty (PTA), and stent placement [17]. However, the most effective treatment approach remains controversial. To the best of our knowledge, there is no previous study comparing the benefits and disadvantages of IVT, IAT, PTA, and stenting in eHAT patients. Thrombolysis is believed to be more effective in fresh clots because of the high water content and relatively fibrin-poor matrix. Hemorrhage is the most common complication, seen in approximately 22% to 46% of patients [17,18]. It is a relative contraindication of thrombolysis in patients who already have internal bleeding or signs of hemorrhage. IAT, PTA, and stenting are procedures that can fail due to technical reasons, and may even cause mechanical injury to the HA [17]. Ueno et al. reported that 45% of patients who underwent HA stenting after liver transplantation developed hepatic arterial complications, including restenosis, HA thrombosis, HA aneurysm, and long-segment stricture [19]. In our routine procedure, PTA and/or stenting are applied in late HA stenosis patients (>1 month after LDLT), in which reoperation becomes difficult due to fibrosis and adhesion over the anastomotic site. In contrast, IVT is easy to perform without risk of arterial injury, but it may be effective in the early stage of thrombus formation. IVT is a safe approach without risk of arterial complications, which can preserve a possible alternative artery for further surgical intervention if necessary. Our results suggest that IVT is a convenient and good option with favorable prognosis for those eHAT patients with only partial arterial occlusion and no other complications in CTA.

According to our results and experience, patient with LDLT should receive intensive DUS once per day for at least 2 weeks for early detection of thrombus formation. Subsequent CTA is necessary in patients with abnormal Doppler waveforms. In eHAT patients with partial occlusion, medical IVT is the first-line treatment. Surgical intervention should be considered if there is no regain of arterial flow after medical thrombolysis or in eHAT patients with total occlusion and/or other complications that need further surgical intervention.

This study has some limitations. First, the limited number of patients limits any conclusions about clinical symptoms, laboratory values, image findings, treatment choices, and any relationships among the above parameters. Second, we only enrolled recipients with postoperative eHAT to emphasize the effect of intensive DUS and subsequent CTA, and those with intraoperative eHAT and postdischarge delayed HAT were not considered. Third, only patients who underwent surgery had a definite diagnosis of eHAT by surgical findings. Occlusion of the HA in CTA is really not a definition or the criterion standard of HAT, although it is one of the most accurate imaging indicators of eHAT. The patients with IVT had no surgical proof of eHAT. eHAT was still be suspected based on imaging findings and regain of arterial flow after mediation.

Conclusions

Intensive post-LDLT bedside DUS is a convenient and sensitive tool for eHAT detection. DUS once a day for at least 2 weeks is an appropriate protocol and is helpful in postoperative care and has long-term benefits. Subsequent CTA gives valid and detailed information on occluded arteries and associated findings, which impact decision-making and are correlated with patient outcome. The post-LDLT DUS has good sensitivity and high diagnostic accuracy in eHAT patients, even in those with only partial occlusion. Continuous monitoring of arterial flow and Doppler waveforms by DUS during IVT treatment avoids unnecessary reoperation and prevents long-term biliary complications.

Acknowledgment

We thank the Liver Transplant Center of Kaohsiung Chang Gung Memorial Hospital and all the subjects who participated in this study.

Conflict of interest

None.
References: