Contrast-enhanced ultrasound for the evaluation of hepatic artery occlusion after liver transplantation

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Abstract

Introduction: Vascular complications after liver transplantation remain a major threat to the survival of recipients. HAT is a major cause of graft loss and patient mortality, with an incidence between 3% to 8% in transplant recipients. Early detection of HAT is critical because urgent revascularization is required to avoid severe graft loss. Although ultrasound is the preferred first-line imaging modality in patients with suspected HAT, the accuracy and positive predictive value of HAT on Doppler US are reported to be low. Moreover, Doppler examination of the hepatic vasculature is time consuming and requires a high level of operator skill. Conventional angiography remains the gold standard for diagnosis. Recently, contrast-enhanced ultrasound (CEUS) has begun providing real-time angiographic-like images of vessels at bed side and allowing the accurate diagnosis of arterial diseases such as hepatic artery thrombosis. The purpose of this study was to evaluate the efficacy of CEUS in detecting HAT after liver transplantation: Materials and Methods: This is a retrospective data of the medical records of patients undergoing Liver transplantation in the Osmania General Hospital, Hyderabad between 2016 to 2018. Status of hepatic vascular assessment following liver transplantation done by conventional Doppler Ultra sonography and Contrast Enhanced Ultrasonography tests were obtained from registries of medical records. Results: 23 cases of post Liver transplantation aged between 4 years and 58 years, with a median age of 30 years were included in the analysis. There were 20 males and 3 females. 14 patients underwent DDLT, 7 patients underwent LDLT, 1 underwent split Liver transplantation and another 1 patient underwent Auto liver transplantation. Doppler US was inconclusive regarding patency of the hepatic artery (HA) circulation in 5 (21.7 %) of 23 transplantsations. CEUS was performed in these 5 patients and detected HA thrombosis (HAT) in 2 cases and patent HA in 3 transplants. These 5 Transplants were confirmed by CT Angiography /conventional Angiography. In the subset of transplantsations examined with CEUS, the sensitivity, specificity and accuracy of CEUS were 100%. CEUS was done at bedside without any Radiation and Nephro toxicity. In approximately 21.7% of cases, conventional Doppler US did not provide sufficient visualization of the HA after liver transplantation. In these cases, correct diagnosis was achieved by supplementary CEUS. Conclusion: CEUS may be a new approach for early diagnosis of postoperative vascular complications after Liver Transplantation, and it can be performed at the bedside. It is safe will not cause any nephron toxicity and Radiation. CEUS is a fast, non-ionizing imaging modality for the initial exclusion of vascular complications after liver transplantation. CEUS shows a high specificity and PPV in the detection of vascular complications. In unclear cases CT still is considered as the gold standard

Keywords: Doppler ultra sound, Contrast-enhanced ultra sound, Hepatic artery thrombosis, Liver transplantation, Angiography.

Introduction

Liver transplantation is a well-accepted therapeutic modality for both acute and chronic liver failure [1]. Vascular complications after liver transplantation remain a major threat to the survival of recipients. Hepatic artery thrombosis (HAT) occurs in 3–8% of the transplant recipients. It may occur within the first 24 h and is an important cause of re transplantation [2–8].
LDLT recipients (more for paediatric LDLT recipients) are more likely to develop vascular complications because of their complex vascular reconstruction and the slender vessels. Early diagnosis and treatment are critical for the survival of graft and recipients.

Usually, conventional Doppler ultrasonography (CDUS) is the initial imaging technique for identification of vascular complications [2,3,7,9,10]. It is mobile can be done bedside, does not involve ionizing radiation, non-invasive and inexpensive.

Recently, contrast enhanced ultrasound (CEUS) has significantly improved the diagnosis of postoperative vascular complications. CEUS improves the detailed vascular tracing and perfusion visualization in both the hepatic artery (HA) and portal vein (PV). This article focuses on the role of Doppler ultrasound and CEUS for early diagnosis of vascular complications after liver transplantation.

**Methods and Materials**

In this study, a two-step approach for assessment of liver vessel patency was performed, first conventional Doppler US, and then, in case of uncertainty, real-time CEUS with a second-generation contrast agent intravenously. In this study, a two-step approach for assessment of liver vessel patency was performed, first conventional Doppler US, and then, in case of uncertainty, real-time CEUS with a second-generation contrast agent intravenously.

**Place of study and type of study:** This is a retrospective data of the medical records of patients undergoing Liver transplantation in the Osmania General Hospital, Hyderabad between 2016 to 2018.

Demographic data, Indications for liver transplantation, type of liver transplantation (DDLT and/or LDLT), Status of hepatic artery flow, Portal vein and Hepatic veins assessment after liver transplantation by conventional Doppler Ultra sonography and Contrast Enhanced Ultrasonography tests were obtained from registries of medical records.

In this study, a two-step approach for assessment of liver vessel patency was performed, first conventional Doppler US, and then, in case of uncertainty, real-time CEUS with second-generation contrast agent intravenously. The radiologists had all been trained to examine liver-transplanted patients with respect to size of the liver and echogenicity of parenchyma, state (open or not) of the HA both intra- and extra-hepatically including measurement of resistive index (RI, normal 0.5–0.7). The normal hepatic artery Doppler waveform should have a rapid systolic upstroke and continuous diastolic flow [9].

Patency and flow direction of portal vein (PV), retrohepatic vena cava and hepatic veins were also evaluated. In cases where the examiner could not find a patent HA with a normal arterial spectral curve, the Doppler US was repeated by another, more experienced radiologist during the same session.

If still in doubt about the patency of the artery, the more experienced radiologist performed CEUS with the same scanner using one or more 2.4 ml doses of a sulfur hexafluoride-containing second-generation contrast agent (SonoVue, Bracco Suisse SA, Switzerland) given intravenously in an antecubital vein with a 5-ml 0.9% saline flush.

A radiologist with 7 years of experience with CEUS at the start of the study performed the majority (90%) of the CEUS examinations with regard to the patency of HA. A dual screen display with the contrast images and low mechanical grayscale image side by side was instructive and often used.

The images were saved as still images and/or video clips. Patients were under medical supervision during and for at least 30 min following the administration of the contrast agent.

**Inclusion criteria:** All post liver transplantation patients whose blood vessel patency assessed by Doppler US and CEUS were included in this study.

**Exclusion criteria:** If any post liver transplantation patient did not undergo CEUS evaluation were excluded from this study.

**Statistical methods:** Continuous data were expressed as median/range and analysed by Kruskal–Wallis test, and categorical variables were expressed as number/percentage and analysed by chi-square test.

The sensitivity, specificity, and accuracy for determination of HA occlusion in the subset of patients examined with CEUS were calculated. Sensitivity was defined as the probability of a positive test in a transplant with an occluded artery.

Specificity was the probability of a negative test in a transplant with an open artery.
Results

23 cases of post Liver transplantation aged between 4 years and 58 years, with a median age of 30 years were included in the analysis. There were 20 males and 3 females.

14 patients underwent DDLT, 7 patients underwent LDLT, 1 underwent split Liver transplantation and another 1 patient underwent Auto liver transplantation.

The indications for liver transplantation are chronic Budd Chiari syndrome in 3, Alcoholic chronic liver diseases in 7, Wilsons disease in 3, Auto immune hepatitis in 1, congenital hepatic fibrosis in 1, Alagille syndrome in 1, Nonalcoholic liver diseases (NASH) in 2, Hepatitis B related CLD in 1, Hepatitis C induced CLD in 1, Primary sclerosing cholangitis in 1 and cryptogenic cirrhosis in 2.

All patients underwent Doppler US twice daily for 10 days following Liver transplantation.

Whenever Hepatic artery, Portal vein or Hepatic veins are not visualized in conventional Doppler US they underwent CEUS. If CEUS also did not show flow in Hepatic artery or Portal vein they underwent CT Angiography / Conventional angiography.

Doppler US was inconclusive with regard to patency of the hepatic artery (HA) circulation in 5 (21.7 %) of 23 transplantations.

CEUS was performed in these 5 patients and detected HA thrombosis (HAT) in 2 cases and patent HA in 3 patients.

These 5 Transplants were confirmed by CT Angiography / conventional Angiography. In the subset of transplantations examined with CEUS, the sensitivity, specificity and accuracy of CEUS were 100%.

CEUS was done at bedside without any Radiation and Nephro toxicity.

In approximately 21.7% of cases, conventional Doppler US did not provide sufficient visualization of the HA after liver transplantation.

In these cases, correct diagnosis was achieved by supplementary CEUS.

Table-1: Showing results of Hepatic artery status with Doppler USG Abdomen, CEUS and CT Angiography/Conventional Angiography.

<table>
<thead>
<tr>
<th>Type of Image</th>
<th>Total number of patients (n=23)</th>
<th>DDLT</th>
<th>LDLT</th>
<th>LTP SPLIT</th>
<th>AUTO LTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Doppler Ultrasonography</td>
<td>23</td>
<td>14</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CEUSG</td>
<td>5</td>
<td>3 (patent HA)</td>
<td>2 (No flow in HA)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CT Angiography / conventional Angiography</td>
<td>6</td>
<td>3 (patent HA)</td>
<td>2 (No flow in HA)</td>
<td>1 Patent IVC, HV</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Showing, Post Liver Transplantation Patients Demographic data, Type of transplantation, Indication and findings of Doppler US, CEUSG and CT Angiography /Conventional Angiography.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Sex/ age</th>
<th>DDLT/LDLT</th>
<th>Indication</th>
<th>USG Doppler</th>
<th>CEUSG</th>
<th>CT Angio / Conventional Angio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/22</td>
<td>DDLT</td>
<td>PSC</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>M/30</td>
<td>AUTO TRANS PLANTATION</td>
<td>Chronic. Budd Chiari syndrome</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>Patent HA, HV and IVC.</td>
</tr>
<tr>
<td>3</td>
<td>M/22</td>
<td>DDLT</td>
<td>Chronic. Budd Chiari syndrome</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>M/40</td>
<td>DDLT</td>
<td>ALCOHOLIC CLD</td>
<td>Not visualized HA</td>
<td>Patent vessels</td>
<td>Patent HA</td>
</tr>
<tr>
<td>5</td>
<td>F/20</td>
<td>DDLT</td>
<td>WILSONS DISEASE</td>
<td>Doubtful HA patency</td>
<td>Patent vessel</td>
<td>Patent HA</td>
</tr>
<tr>
<td>6</td>
<td>M/29</td>
<td>DDLT</td>
<td>Chronic. Budd Chiari syndrome</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>M/41</td>
<td>DDLT</td>
<td>Alcoholic CLD</td>
<td>HA Not visualised</td>
<td>HA flow visualized</td>
<td>Patent HA</td>
</tr>
<tr>
<td>8</td>
<td>M/40</td>
<td>DDLT</td>
<td>AUTO IMMUNE CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>M/40</td>
<td>DDLT</td>
<td>CRYPTOGENIC</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>M/56</td>
<td>DDLT</td>
<td>Alcoholic CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>M/53</td>
<td>DDLT</td>
<td>Alcoholic CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>M/32</td>
<td>DDLT</td>
<td>Alcoholic CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>F/11</td>
<td>LDLT</td>
<td>Wilsons</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>M/56</td>
<td>LDLT</td>
<td>HBV CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>M/7</td>
<td>LDLT</td>
<td>Cong. Hepatic Fibrosis</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>M/58</td>
<td>DDLT</td>
<td>NASH</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>M/50</td>
<td>LDLT</td>
<td>Alcoholic CLD</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>M/56</td>
<td>LDLT</td>
<td>Wilsons</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>M/13</td>
<td>SPLIT</td>
<td>Cryptogenic</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>M/40</td>
<td>DDLT</td>
<td>NASH</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>M/45</td>
<td>DDLT</td>
<td>Alcoholic</td>
<td>HA, PV, IVC and HV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>M/54</td>
<td>LDLT</td>
<td>HCC with HCV CLD</td>
<td>HA not visualised</td>
<td>No flow in intra hepatic HA</td>
<td>HA Block at anastomosis</td>
</tr>
<tr>
<td>23</td>
<td>M/9</td>
<td>LDLT</td>
<td>Alagille syndrome</td>
<td>HA not visualised</td>
<td>NO flow in HA</td>
<td>HA Block at anastomosis</td>
</tr>
</tbody>
</table>
Discussion

HAT is a major cause of graft loss and patient mortality, with an incidence between 3% to 8% in adult transplant recipients [2,3]. Early detection of HAT is critical because urgent revascularization is required to avoid severe graft loss. Although ultrasound is the preferred first-line imaging modality in patients with suspected HAT, the accuracy and positive predictive value of HAT on CDUS are reported to be only 64%-82% and 64%-68%, respectively [17,18]. Moreover, Doppler examination of the hepatic vasculature is time consuming and requires a high level of operator skill.

CEUS has been reported to effectively improve flow visualization of the hepatic artery [4,19] and to shorten the scanning time in compared with CDUS [28], with a 100% sensitivity and 97.8% accuracy for the detection of HAT[20].

In this study, a two-step approach for assessment of liver vessel patency was performed, first conventional Doppler US, and then, in case of uncertainty, real-time CEUS with a second-generation contrast agent intravenously. By this approach, 2 HA occlusions that
had occurred in 23 liver transplantations were detected. A prevalence of HA occlusion of 8% agrees with previous studies [2-8]. HAT is more common in LDLT than DDLT due to slender branches. In our series HAT was noticed in 2 cases of LDLT and none in DDLT. In these patients, this serious complication could be corrected surgically without undue delay because of bed-side documentation of an occluded HA with CEUS. There was no false positive diagnosis of HA occlusion, and in 5 doubtful cases (according to Doppler US), an open artery could be visualized by CEUS in 3, thus avoiding laparotomy or other more expensive imaging procedures. In most cases, conventional Doppler ultrasound was sufficient to document an open HA after liver trans- plantation. Supplementary CEUS provided correct Information in the remaining 21.7% of transplantations. In accordance with previous studies, CEUS improved flow visualization of the HA and PV and correctly differentiated between thrombosis and a patent artery in patients without HA flow at conventional Doppler US [4,6,11-13]. The use of CEUS avoided the need for invasive arteriography in 62.9% of such cases. Thus, HAT has evolved into the most important CEUS application in liver transplantation.

Previous studies have used conventional angiography as a reference standard, whereas we used clinical follow up including repeating Doppler US and, in selected cases, CT angiography /conventional Angiography. Microbubble contrast was only given to the patients in whom the HA was not visualized with certainty. The most important advantage of CEUSis it can be done in the immediate postoperative period (<24 h) in the operating theatre or in the intensive care unit where conditions are far from ideal. In general, when doubtful about patency of hepatic vasculature with conventional Doppler, CT Angiography/ conventional Angiography may be considered, but may be more cumbersome and time- consuming to perform postoperatively than CEUS. CEUS improved visualization of both extra- and intra-hepatic parts of the HA. This quality of CEUS is particularly valuable in the early postoperative phase when the often-weak Doppler signals from intrahepatic arteries are sometimes obscured by portal venous flow. Doppler US and CEUS should therefore be considered as complementary rather than competitive methods. The main advantage of this study is it will not cause any nephro toxicity and can be done at bed side unlike CT /Conventional angiography. The main drawbacks of this study is retrospective study and hepatic artery stenosis cannot be detected as clearly as CT angiography / conventional angiography.

**Conclusion**

The conventional Doppler US proved sufficient to document open vessels after liver transplantation in most cases. But Supplementary CEUS provided correct information in the remaining doubtful patients in the operation theatre or in the intensive care unit where conditions are far from ideal.

However, there is a need of randomized control studies that would effectively verify the conclusions of this study.

**Message of this study:** CEUS is an ideal bed side investigation of choice when conventional doppler US is doubtful about hepatic vasculature patency after liver transplantation particularly in the Operation theatre and ICU where conditions are far from ideal.

**Authors Contribution**

Author 1. Prepared the manuscript and performed all surgeries.

Author 2. Helped in Conventional doppler and CEUS assessment of liver transplant patients.

Author 3. Helped in Conventional doppler and CEUS assessment of liver transplant patients.

Author 4. Supervised the paper and involved in patient care of these patients.

Author 5. Helped in Conventional doppler and CEUS assessment of liver transplant patients.

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**Permission of IRB:** Yes

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