30 درصد تخفیف نوروزی ویژه کارگاه‌ها و فیلم‌های آموزشی

اصول تنظیم قراردادها
پروریزال نویسی
آموزش مهارت‌های کاربردی در ندوین و چاب مقاله
Current State of Art Management for Vascular Complications after Liver Transplantation

S. Kamran Hejazi Kenari¹, Asha Zimmerman¹, Mohammad Eslami², Reza F. Saidi¹,*

ABSTRACT

Vascular complications by compromising the blood flow to the allograft can have significant and sometimes life-threatening consequences for the patient. High level of suspicion and aggressive utilization of diagnostic modalities can lead to early diagnosis and salvage of the allograft. This review will summarize the current trends in the management of vascular complications after liver transplantation. Current trends show an increase in the utilization of endovascular interventions initially to address vascular complications after liver transplantation. Operative repair still has its major role, especially if endovascular procedures fail.

KEYWORDS
Liver Transplantation; Vascular Complications; Endovascular interventions; Outcomes

INTRODUCTION

Vascular complications are rare but serious causes of morbidity and mortality after liver transplantation (LT). Bleeding, stenosis, thrombosis, and aneurysm can arise at any of the vascular anastomoses. The incidence is generally about 8-15%¹. However, this rate can be as high as 20%,² especially in cases such as split liver transplantation or LDLT.²–⁸ Hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) interrupt the allograft’s blood supply and produce early allograft loss, long-term dysfunction, or even patient’s death.

Arterial complications are the most common (5-10%) vascular complication after LT. Early HAT generally needs re-transplantation while venous complications including portal and caval problems are less frequent (each about 2%) and can usually be treated by surgical or endovascular intervention.¹ Vascular problems must be treated aggressively, particularly HAT and PVT which can interrupt the liver’s blood supply and cause dysfunction and even graft loss or death.⁹ Many factors have been described as the cause of these vascular complications such as technical problems in anastomosis, problems in allograft anatomy which may result in vascular kinking, and differences in the size of donor’s and recipient’s vessels.³¹⁰¹¹ Similar to other arterial anastomoses, the process of intimal hyperplasia may affect the patency of the arterial anastomosis in long term.
Arterial Complications

Arterial problems are the most common vascular complications after LT. These problems include HAT, hepatic artery stenosis (HAS), and hepatic artery kinks (HAK). HAS and HAT can lead to allograft ischemia, which carries a high mortality and morbidity rate. Arterial complications are often diagnosed firstly by Duplex followed by CT angiography. Role of Doppler ultrasonography in the early diagnosis of HAS has been evaluated in several reports. Doppler ultrasonography showed a sensitivity of 100%, a specificity of 99.5%, a PPV of 95% and NPV of 100%, and overall accuracy of 99.5% in early diagnosis of HAS. Many protocols also use angiography to confirm the diagnosis.

Many patients with HAS are asymptomatic and most commonly present only with abnormal liver function tests (LFT). Compared with HAST (hepatic artery stenosis), risk of development of biliary complications are less with HAS. Balloon angioplasty can be an effective treatment option in these cases. Anastomotic stenosis is the most common place for development of hepatic artery stenosis within 3 months after LT.

Hepatic Artery thrombosis represents more than 50% of all arterial complications following LT. HAT presentations may be a continuum from only abnormal transaminase, to fever and sepsis due to biliary dysfunction and graft failure. Based on the interval between LT and development of thrombosis, HAT can be divided into early HAT (within 4 weeks) and late HAT. The rate of re-transplantation in untreated HAT is 25-83% while it is 28-35% in patients who underwent re-vascularization. Early HAT may be the result of technical problems and can have dramatic presentation. Because early HAT has a higher mortality compared with late HAT, related to the ischemia/necrosis of bile duct and subsequent sepsis, an emergent intervention is required. Earlier studies showed a higher rate of early HAT after LT probably due to limited initial experience and also the insidious nature of late HAT. Up to 50% of patients with late HAT can be asymptomatic with only elevated LFT. Symptomatic patients often present with biliary complications with recurrent cholangitis, abscess and biliary leakage or stricture, and the presentation may be insidious. Late HAT is usually due to ischemic or immunologic injuries. Patients with late asymptomatic HAT can be initially treated with biliary stent placement and/or endovascular interventions.

Duffy and colleagues evaluated 4,234 LT from 1984 to 2007. Of them 203 (5%) developed HAT including 133 early and 70 late HAT. Occurrence of HAT was 3.9% in adults. Overall 90 patients were treated with surgical exploration, thrombectomy, or anastomotic revision. Nine patients were treated with catheter-based thrombolysis and 13 patients received anticoagulation. Of the patients with early HAT who underwent thrombectomy and anastomotic revision, only 9 (10.5%) had graft salvage and the remaining patients needed re-transplantation. Overall, re-transplantation was necessary in 153 (75%) patients with HAT. However re-transplantation after HAT had a better survival rate compared with revision or thrombolysis.

Factors associated with HAT can be divided into several categories (table 1). Technical problems are mainly associated with early HAT. Positive CMV antibody in donor and negative CMV in recipients have been shown to be associated with late HAT. On the other hand, while some authors believe that HAS and HAK are the initiating factor, others suggest perioperative hypercoagulable state as a possible underlying cause. Other factors leading to HAT include longer cold ischemia, longer operative time, shorter warm ischemia, transfusion of more than 6 units of whole blood and/or ≥ 15 units of fresh frozen plasma (FFP).

Use of aortic conduit may also be a risk factor for development of HAT. While some earlier studies indicate that there is no difference in the results when aortic conduits are used, more recent studies emphasize a higher risk of HAT in those with aortic conduits. Duffy and co-workers also reported a higher incidence of HAT with aorto-hepatic grafting compared with standard reconstructions from the celiac trunk. However, other studies reported no difference between these two approaches. Ni-
kitin and colleagues, for example, reported graft survival rate of 59% with arterial conduit and 67% without the conduit in 5-year follow-up and 33% and 35%, respectively, in 15 years of follow-up. With 20 years of follow-up, there was no significant difference in graft or patients’ survival or incidence of hepatic artery or biliary complications.

Other factors unrelated to operation or operative technique may also play a role in developing HAT. For example, use of transarterial chemoembolization (TACE) as a “bridging” or “down staging” therapy before transplantation for treatment of hepatocellular carcinoma (HCC) can induce periarterial inflammation which in turn can lead to HAT.

Although urgent re-transplantation is considered the main treatment for early HAT, endovascular interventions including PTA, intra-arterial thrombolysis (IAT) in selective cases, and stent placement may be alternative treatments. Currently, in many centers, percutaneous transluminal angioplasty (PTA) and stent placement are tried first to resolve the problem, while solitary short stenotic lesions are usually most amenable to PTA, angioplasty has a high success rate in tandem lesions.

It is also important to consider that while recent reports have shown encouraging results of endovascular interventions, the efficacy and risk of complications of these procedures particularly potential risk of hemorrhage are still controversial and in some cases these endovascular interventions are ineffective and surgical intervention (including anastomotic reconstruction or even re-transplantation) must be applied. The complications of PTA include thrombosis, vascular dissection or even rupture.

Intra-arterial infusion of thrombolytic agents can also be used in selective cases of HAT. Intra-arterial thrombolysis (IAT) is contraindicated in patients who has had recent (≤2 weeks) abdominal operations. It is necessary to carefully monitor the use of thrombolytic agents by evaluating either fibrinogen level, prothrombin time (PT), or activated partial thromboplastin time (aPTT). Hemorrhage is the most common complication of IAT. Singhal and co-workers performed a systematic literature search on endovascular treatment of HAT, which had been done before June 2009. In their review the success rate of thrombolysis was 68% (47 out of 69) and 29 out of the 47 patients underwent further interven-

<table>
<thead>
<tr>
<th>Table 1: Risk factors associated with development of hepatic artery thrombosis after liver transplantation. 6,9,16,30,34–41</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor factors</strong></td>
</tr>
<tr>
<td>Abnormal donor arterial anatomy</td>
</tr>
<tr>
<td>CMV (+) donor while recipient is CMV(-)</td>
</tr>
<tr>
<td><strong>Recipient factors</strong></td>
</tr>
<tr>
<td>Abnormal recipient arterial anatomy</td>
</tr>
<tr>
<td>Immunological or genetic factors</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Celiac stenosis or compression by median arcuate</td>
</tr>
<tr>
<td>ligament</td>
</tr>
<tr>
<td>Multiple rejections</td>
</tr>
<tr>
<td><strong>Peri-operative factors</strong></td>
</tr>
<tr>
<td>Cold ischemia time</td>
</tr>
<tr>
<td>Warm ischemia time</td>
</tr>
<tr>
<td>Ischemia-reperfusion injury</td>
</tr>
<tr>
<td><strong>Operational factors</strong></td>
</tr>
<tr>
<td>Technical problems in creating an anastomosis</td>
</tr>
<tr>
<td>Performing complex back-table arterial reconstruction</td>
</tr>
<tr>
<td>Increased number of FFP and/or whole blood transfusion</td>
</tr>
<tr>
<td>Aortic conduit for arterial re-construction</td>
</tr>
<tr>
<td>Roux-en-Y biliary reconstruction</td>
</tr>
<tr>
<td>Roux-en-Y biliary reconstruction</td>
</tr>
<tr>
<td><strong>Post-operative factors</strong></td>
</tr>
<tr>
<td>Bile leak</td>
</tr>
<tr>
<td>Cholangitis</td>
</tr>
<tr>
<td>Re-laparotomy</td>
</tr>
</tbody>
</table>

Studies have shown that both PTA and stent placement have comparable results for treatment of HAS (table 2). According to some reports use of PTA for management of HAS can reduce the rate of HAT more than threefold. While solitary short
tion including PTA or stent placement or both. Additionally, percutaneous mechanical thrombectomy of HAT can be an alternative when IAT is contraindicated. In these cases, the thrombus is dissolved and removed by intraluminal suction device.

Vascular complications in patients receiving live donor liver transplantation (LDLT) are unique to these complicated reconstructions. These patients have a higher rate of vascular complications,\(^48\) because of the complexity of vascular reconstruction of smaller and shorter vessels.\(^49\) In recipients of LDLT, the hepatic artery is short and surgical field is deep and the graft artery’s anatomical arrangement may be different from the recipient’s hepatic artery.\(^50\) These vascular complications expose the recipients of LDLT to a higher risk of developing biliary leakage, resistant infection, and other morbidities.\(^51\) HAT can be developed in few hours after the LDLT.\(^52\) There are also reports of simultaneous HAT and PVT following LDLT, which is an ultimately fatal complication.\(^53\) Careful perioperative evaluation and intraoperative microsurgical technique for vascular reconstructions can reduce the chance of vascular complications following LDLT.\(^49\) Yan and co-workers\(^54\) reported their experience in 101 HA reconstruction in LDLT using microsurgical techniques. Only 2 patients (2%) in that group developed HAT. There are also several recent studies that showed excellent results after endovascular interventions for treatment of arterial complications following LDLT.\(^58,49,51–66\) Furuta and colleagues also reported using of microsurgical techniques to create 44 artery anastomoses in 40 LDLT patients. They dissected the recipient arteries that were slightly smaller than the graft’s artery and created an end-to-end anastomosis. No decreases in the arterial blood flow or HAT were reported.\(^50\)

**Vascular Complications after Liver Transplantation**

<table>
<thead>
<tr>
<th>Author/ref.</th>
<th>Year published</th>
<th>Number of cases (EP)</th>
<th>Type of vascular problem</th>
<th>Endovascular intervention(s)</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orons(^59)</td>
<td>1995</td>
<td>21</td>
<td>HAS</td>
<td>PTA</td>
<td>81% (17/21)</td>
</tr>
<tr>
<td>Abbasoglu(^60)</td>
<td>1997</td>
<td>6</td>
<td>HAS</td>
<td>PTA</td>
<td>100%</td>
</tr>
<tr>
<td>Saad(^46)</td>
<td>2005</td>
<td>42</td>
<td>HAS</td>
<td>PTA</td>
<td>81% (34/42)</td>
</tr>
<tr>
<td>Jeon(^41)</td>
<td>2008</td>
<td>4</td>
<td>HAT</td>
<td>Catheter-directed thrombolysis</td>
<td>50%</td>
</tr>
<tr>
<td>Jeon(^41)</td>
<td>2008</td>
<td>19</td>
<td>Peritoneal hemorrhage</td>
<td>Trans-catheter arterial embolization</td>
<td>84% (16/19)</td>
</tr>
<tr>
<td>Jiang(^66)</td>
<td>2008</td>
<td>3</td>
<td>HAT, HAS and HAP</td>
<td>Thrombectomy, Balloon angioplasty/stent placement and embolization (respectively)</td>
<td>100%</td>
</tr>
<tr>
<td>Chen(^62)</td>
<td>2009</td>
<td>20</td>
<td>HAS</td>
<td>PTA + Stent placement</td>
<td>100%</td>
</tr>
<tr>
<td>Maruzzelli(^44)</td>
<td>2010</td>
<td>25</td>
<td>HAS</td>
<td>PTA or stenting</td>
<td>96% (24/25)</td>
</tr>
<tr>
<td>Pérez-Saborido(^5)</td>
<td>2011</td>
<td>4</td>
<td>HAS</td>
<td>Angioplasty and stent placement</td>
<td>25%</td>
</tr>
<tr>
<td>Sabri(^65)</td>
<td>2011</td>
<td>35</td>
<td>HAS</td>
<td>For HAS: balloon angioplasty/stent placement</td>
<td>91%</td>
</tr>
<tr>
<td>Sabri(^65)</td>
<td>2011</td>
<td>6</td>
<td>HAT</td>
<td>Catheter-directed thrombolysis</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>Kim(^58)</td>
<td>2011</td>
<td>6</td>
<td>HAT, HAS</td>
<td>3 IAT (for HAT) 3 PTA (for HAS)</td>
<td>100%</td>
</tr>
<tr>
<td>Abdelaziz(^64)</td>
<td>2012</td>
<td>11</td>
<td>HAT</td>
<td>IAT or PTA</td>
<td>82% (9/11)</td>
</tr>
<tr>
<td>Hamby(^66)</td>
<td>2013</td>
<td>35</td>
<td>HAS</td>
<td>PTA alone or primary stent placement</td>
<td>97%</td>
</tr>
<tr>
<td>Sommacale(^67)</td>
<td>2013</td>
<td>37</td>
<td>HAS</td>
<td>Stent placement</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Summary of studies with utilization of endovascular interventions for arterial complications after liver transplantation.

Venous Complications

Venous complications after LT include caval/hepatic vein and portal problems. In clinical settings, portal vein stenosis leads to portal vein hypertension, which manifests with ascites, anemia, splenomegaly, hypersplenism, and GI bleeding.\(^44,68–70\) Hepatic vein obstruction is clinically similar to Budd-Chiari syndrome.\(^3\) Hepatic vein outflow ob-
struction (HVOO) is a general term reflecting any obstruction of the HV caused by either compression and twisting of the anastomosis resulted from graft regeneration or by intimal hyperplasia and fibrosis at the anastomotic sites.\textsuperscript{71}

There are many reports regarding the incidence and treatment of venous complications after LDLT.\textsuperscript{48,53,57,71–75} Although the incidence of venous complications can be even more than 2 times higher in recipients of LDLT,\textsuperscript{48} acceptable long-term graft and patient’s survival can be achieved after endovascular or operational treatments. In a study by Kyoden and co-workers 5-year survival rate after portal vein complications were 77\%.\textsuperscript{73} The success rate of endovascular interventions for the treatment of venous complications varies from 60\% to 100\%.\textsuperscript{71–73}

Factors associated with PVT include technical problems, small diameter of the portal vein (< 5 mm), previous splenectomy, simultaneous thrombectomy for pre-existing PVT and use of venous conduits for portal vein reconstruction.\textsuperscript{9,76–79} Additionally, longer cold ischemia time (>12 h) can be a risk factor for developing venous problems. This can be due to difficulties in venoplasty (and more manipulation) before anastomosis.\textsuperscript{71} Kyoden and colleagues analyzed the outcome of 310 LDLT in their institution.\textsuperscript{73} Portal vein complications were identified in 28 recipients. Presence of PVT at the time of LDLT, smaller graft size, and use of vein grafts were the risk factors for PV complications. Additionally they found out that the use of jump or interposition cryo-preserved vein grafts predisposed to the occurrence of late, but not early, PV complications.\textsuperscript{73}

Use of cryopreserved vein for portal conduits has been shown to be associated with portal vein stenosis.\textsuperscript{80} In a study by Buell and co-workers,\textsuperscript{80} use of cryopreserved vein for portal conduit led to 6.3\% PVS, which decreased to 1\% when cryopreserved vein was not used. They showed that the use of segmental grafts without venous conduits did not cause a significant increase in the rate of long term venous complication.

Pre-existing venous complications can also cause post-operative PVS and PVT. Lerut and colleagues\textsuperscript{10} reported their experience of 393 LT from 1980 to 1984. Nine out of 313 patients (2.9\%) had pre-existing vena cava abnormalities, which needed adjustment during operation. These included absent retro-hepatic IVC (n=2), extra-hepatic IVC (n=2), absent SVC (n=1), thrombosis of IVC (n=2), and aneurysm of IVC (n=2). Additionally, 51 patients (16.3\%) had pre-existing portal vein abnormalities, which included thrombosis (n=22), hypoplasia (n=20), phlebosclerosis (n=8), and absent portal vein (n=1). These preoperative conditions may necessitate adjunct procedures at the time of transplantation such as thrombectomy and retrograde dissection of the abnormal portal vein to the confluence of the splenic and superior mesenteric veins. The graft portal vein is then anastomosed to this confluence directly or with a graft of the donor’s iliac vein, pulmonary artery, or IVC. Seven patients developed post-operative portal vein thrombosis. Four of these patients had an early convalescence. Portal flow was restored in only one of them. These 4 patients had a pre-existing and undiagnosed thrombosis of the portal vein, splenic vein, or superior mesenteric vein. Overall the incidence of thrombosis of the reconstructed portal vein was only 1.8\%. Only 3 patients (0.8\%) developed post-operative IVC thrombosis, all at the lower IVC anastomosis.\textsuperscript{10}

Compared with arterial problems, venous complications usually have a better response to endovascular interventions such as angioplasty or stent placement (table 3). Transcatheter endovascular procedures are now considered as the first line of treatments for post-transplant portal vein complications and many studies showed the high successful results.\textsuperscript{68,81–85} The initial success rate of hepatic vein PTA is higher than 80\%.\textsuperscript{3} The standard approach for treatment of portal vein complications is via transhepatic access of intrahepatic branch of portal vein, however in case of concurrent portal vein thrombosis this approach is challenging and percutaneous trans-splenic access can be substituted, particularly in patients with short occluded portal vein branches.\textsuperscript{16,77,78,81-92}
The use of anticoagulants after endovascular procedures for venous complications is controversial. While some surgeons use heparin for 1-3 days postoperation the others use it just at the time of surgery. Aspirin is usually used continuously afterward. It is also important to know that re-transplantation after PVT particularly an extensive one, is more challenging than re-transplantation after HAT. The reason is that re-transplantation after PVT requires patent mesenteric graft inflow to provide hepatotrophic factors which is not always easy in such patients.

Aneurysmal complications

Aneurysm and pseudoaneurysm of the hepatic artery (HA) are very rare complications after LT. The rate of post-operational aneurysm or pseudoaneurysm of is much less than other post-transplant vascular complications but they are associated with high mortality (>50%). These complications generally require emergency surgical or angiographic interventions. The diagnosis is usually made by splanchnic angiography or perfusion angiosonography. Aneurysmal complications can be divided to extra- and intrahepatic complications. The most common presentation of extrahepatic aneurysm or pseudoaneurysm is hypotension following its rupture. Bleeding can happen into gastrointestinal system or into peritoneal cavity. They can also be presented by the signs of biliary compression and obstruction. Intrahepatic arterial aneurysms are most frequently iatrogenic and happen following liver biopsy or stent placement. While many of these patients can be treated by coil embolization in case of bleeding and hemodynamic shock, urgent laparotomy is required.

Aneurysmal complications can be treated by either surgical or endovascular procedures. Both surgery and angioembolization are equally effective for hepatic artery pseudoaneurysm. However, patients who undergo angioembolization have more rapid bleeding control, shorter hospital stay, and less transfusion requirements.

In summary, the incidence of vascular complications reported in the literature varies widely among centers. Despite technical progress, vascular complications are still a significant determinant of allograft loss, increasing postoperative morbidity and mortality. Arterial complications are more common, occur early in the postoperative period, and are associated with high rates of graft loss and patient mortality. Conversely, venous complications are less frequent, occur late in the postoperative period, and have no significant effect on graft loss or mortality rates. Strategies for identification and mitigation of risk factors, prevention of technical complications, and protocols for early detection of vascular complications may reduce mortality, morbidity, and the need for re-transplantation. Current trends showed an increase utilization of endovascular interventions initially to address vascular complications after LT with good success. Operative repair still has its role, especially if endovascular procedures fail.

Table 3: Summary of studies with utilization of endovascular interventions for venous complications after liver transplantation

<table>
<thead>
<tr>
<th>Author/ref.</th>
<th>Year published</th>
<th>Number of cases</th>
<th>Type of vascular problem</th>
<th>Endovascular intervention(s)</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin</td>
<td>2006</td>
<td>11</td>
<td>Interposition vein graft (IVG) stenosis</td>
<td>Stent placement</td>
<td>10/11 (91%)</td>
</tr>
<tr>
<td>Yang</td>
<td>2009</td>
<td>6</td>
<td>Intra-operative HV tension, HVS, PVS</td>
<td>Balloon dilation and stent placement</td>
<td>100%</td>
</tr>
<tr>
<td>Cheng</td>
<td>2010</td>
<td>16</td>
<td>PVS and PV occlusion</td>
<td>Stent placement</td>
<td>68.8% (11/16)</td>
</tr>
<tr>
<td>Pérez-Saborido</td>
<td>2011</td>
<td>6</td>
<td>PV, PVS and Caval complications</td>
<td>Angioplasty and stent placement</td>
<td>83% (5/6)</td>
</tr>
<tr>
<td>Umehara</td>
<td>2012</td>
<td>5</td>
<td>HV outflow obstruction</td>
<td>Balloon angioplasty and stent placement</td>
<td>100%</td>
</tr>
</tbody>
</table>
CONFLICT OF INTEREST
The authors declare no conflict of interest related to this work.

REFERENCES


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