Transjugular Intrahepatic Portosystemic Shunt Placement for Refractory Ascites: Review and Update of the Literature

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Semin Intervent Radiol 2018;35:165–168

Abstract

Ascites is the most common complication of cirrhosis, impairs quality of life, and carries a poor prognosis. Transjugular intrahepatic portosystemic shunt (TIPS) is a well-validated therapy for refractory ascites and is superior at reducing the accumulation of fluid compared with paracentesis. More recent evidence has shown that TIPS also provides an improved transplant-free survival compared with paracentesis. To maximize the clinical efficacy and survival advantage, proper patient selection is crucial. While current guidelines recommend that elective TIPS for ascites should be performed only in patients with MELD $\leq$ 18, recent literature suggests that elective TIPS safely and effectively controls ascites and potentially provides a survival advantage in patients with higher MELD scores ($\leq$ 24). The evolution of these findings likely represents the combination of improved medical management of cirrhotic patients, improved devices, and a better knowledge of selection criteria for potential TIPS patients. This article will review the pathophysiology and management of ascites, with a focus on the evidence supporting TIPS placement for refractory ascites.

Keywords
- TIPS
- portal hypertension
- refractory ascites

Objectives: Upon completion of this article, the reader will be able to identify the role of TIPS for refractory ascites, including the clinical efficacy, effect on survival, and patient selection criteria.

Accreditation: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

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Ascites is the most common complication of cirrhosis, with more than 50% of these patients developing the condition within 10 years of diagnosis.[1] The development of ascites impairs quality of life and carries a poor prognosis, with a 1-year transplant-free survival (TFS) of 63%.[2] This article will review the pathophysiology and management of ascites, with a focus on the evidence supporting transjugular intrahepatic portosystemic shunt (TIPS) placement for refractory ascites.

Pathophysiology and Medical Management of Ascites

In the United States, the most common cause of ascites is cirrhosis, which leads to both mechanical and biochemical changes that result in fluid accumulation. Ascites develops in the setting of elevated pressure within the portal system, generally after the portal pressure exceeds 12 mm Hg.[3,4] At

Issue Theme Update on Portal Hypertension; Guest Editor, Bartley G. Thornburg, MD

DOI https://doi.org/10.1055/s-0038-1661347.
ISSN 0739-9529.

this level, vasodilators including nitric oxide are released into the splanchnic circulation. Structural sinusoidal obstruction (e.g., cirrhosis) in conjunction with splanchnic vasodilation subsequently leads to the release of systemic vasoconstrictors, predominantly modulated by the renin–angiotensin system and antidiuretic hormone. This systemic release results in significant water and sodium retention, in turn leading to increased extracellular fluid volume and progression of ascites.[5,6]

Initial medical management of ascites includes sodium restriction (<2 g/day), alcohol abstinence, treatment of the underlying liver disease, and diuretic therapy. A typical diuretic regimen consists of spironolactone and furosemide, beginning at 100 and 40 mg, respectively, with dose escalation as needed and tolerated.[7]

Refractory ascites is accumulation of fluid despite maximum diuretic use,[8,9] which occurs in 5 to 10% of patients with cirrhosis and is usually due to the progression of underlying liver disease.[1,10,11] In the setting of refractory ascites, additional therapies must be considered.

Treatment of Refractory Ascites

Treatment options for refractory ascites include large-volume paracentesis (LVP) with albumin replacement, insertion of a TIPS, placement of a Denver peritoneovenous shunt, and liver transplantation.[10] Liver transplantation is the ultimate treatment for cirrhosis and ascites; however, organ supply substantially limits this option. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the International Club of Ascites, first-line treatment of refractory ascites is LVP.[6,8,12] However, as LVP does not eliminate the underlying cause of ascites formation, it may lead to poor compliance and reduced quality of life.[13] Current guidelines recommend consideration of TIPS placement if more than three paracenteses are performed per month or if paracentesis is not tolerated by the patient.[8]

Efficacy of TIPS for Refractory Ascites

TIPS placement reduces sinusoidal and portal pressure, which helps alleviate fluid retention. Additionally, the presence of a TIPS increases right heart preload, which in turn increases cardiac output, leading to improved natriuresis and fluid excretion. The combination of these effects works to alleviate ascites. The efficacy of TIPS placement for the control of recurrent ascites has been well validated by several randomized controlled trials (RCTs) and meta-analyses. The meta-analyses comparing the use of TIPS to paracentesis in cirrhotic patients with refractory ascites demonstrate that TIPS provided significantly improved control of refractory ascites compared with paracentesis.[2,14–16] However, the studies showed that the portosystemic shunting that leads to ascites control also contributes to an increased incidence or severity of hepatic encephalopathy. A disadvantage of the meta-analyses is that they evaluated the use of bare metal TIPS stents, which does not reflect current clinical practice. Multiple studies have demonstrated improved patency and outcomes with covered stent grafts, which have since become the standard of care.[17–20] A recent RCT investigated the use of covered stents for refractory ascites and similarly found improved control of ascites compared with paracentesis.[21] Interestingly, this study demonstrated that the patients treated with covered TIPS and LVP had the same incidence of hepatic encephalopathy during follow-up.

Survival after TIPS for Refractory Ascites

The efficacy of TIPS in the control of refractory ascites is well established; however, until recently, the effect of TIPS on survival has been more controversial. Early meta-analyses in 2004–2005 did not show a significant difference in survival between patients who underwent TIPS and patients who underwent recurrent LVP for refractory ascites.[15,16,22] However, a follow-up meta-analysis by Salerno et al in 2007 analyzed individual patient data from prior RCTs and found that patients who underwent TIPS had a significantly better TFS than patients who received LVP.[2] The average TFS at 1 year was 63.1% for patients who had TIPS placement compared with 52.5% for patients who underwent paracentesis ($p = 0.035$). Similarly, a meta-analysis by Bai et al in 2014 showed a survival advantage for TIPS versus LVP.[14] A limitation is that both meta-analyses analyzed RCTs which were primarily evaluating efficacy of ascites control rather than survival. A recent multicenter prospective trial by Bureau et al in 2017 randomized 62 patients with refractory ascites to either TIPS placement with a covered stent graft (Viatorr; Gore, Flagstaff, AZ) or recurrent LVP.[21] The study is notable because the primary endpoint was TFS (rather than control of ascites) and the use of covered stents reflects the current practice of TIPS placement. The study showed significantly improved TFS at 1 year in the TIPS group (93%) compared with the LVP group (52%, $p = 0.003$). Additionally, in the multivariate analysis, the only factor that was significantly associated with higher TFS was TIPS placement. The authors concluded that TIPS should be preferred to LVP for the treatment of refractory ascites in select patients. In another prospective randomized trial, Narahara et al demonstrated improved 1- and 2-year survival rates for patients with good hepatic and renal function who underwent TIPS for refractory ascites compared with LVP.[23] The evolution of the survival advantage demonstrated in these meta-analyses and trials likely reflects improvements in TIPS techniques, including the use of covered stents, improved medical management, and a better understanding of patient selection criteria for TIPS placement.

Patient Selection

TIPS is not recommended for the management of ascites in patients with severe liver failure, uncontrolled systemic infection, uncontrolled encephalopathy, or severe cardiopulmonary diseases (e.g., congestive heart failure or severe pulmonary hypertension). The assessment of liver failure severity can be performed using multiple scoring systems,

but the most commonly used is the model for end-stage liver disease (MELD). The MELD score was initially developed to predict early mortality after TIPS placement.[24] Soon after its development, it was found to be an accurate predictor of mortality in all patients with end-stage liver disease, and it evolved into the disease severity index that is currently used today.[24,25] The MELD score remains a key determinant of a patient's eligibility for elective TIPS placement for refractory ascites. Initial studies which investigated the relationship between MELD score and mortality after TIPS determined that patients with a MELD score above 18 had a significantly higher early mortality.[25–28] Current AASLD guidelines (updated in 2009) reflect these findings and recommend for patients with MELD greater than 18 that TIPS should be placed only in the absence of other options.[29] However, more recent literature suggests that the MELD range for elective TIPS may be expanded. A retrospective review showed that early death after elective TIPS was highest in patients with MELD greater than 24.[30] Additionally, in the meta-analysis by Salerno et al, it was shown that compared with paracentesis, the benefit of TIPS on TFS can be seen across all MELD scores.[2] In 2017, Ascha et al conducted a study evaluating the effect of TIPS on TFS in patients with MELD $\geq$ 15, compared with a cohort matched for age and MELD who did not receive a TIPS. The study found that after the first 2 months, the TIPS cohort had a 56% lower risk of death or need for liver transplantation compared with the cohort that did not receive a TIPS.[31] Similarly, Spengler et al recently analyzed the interaction between MELD score and TIPS placement in patients with refractory ascites.[32] Compared with those who did not receive a TIPS, as MELD increased, the risk of death was progressively lower than expected in patients who received TIPS. Patients with high MELD scores (>18) who received a TIPS had a mortality risk that was 51% lower than expected in the first 6 months following TIPS placement. The evolution of the literature regarding selection criteria for TIPS placement parallels the recent data of improved survival after TIPS placement, and also likely reflects the evolution of medical management and the improved patency of current stent grafts compared with prior bare metal stents.

TIPS for Ascites after Liver Transplantation

Liver transplantation is the ideal treatment for cirrhosis and its accompanying complications. Portal hypertension after liver transplantation may occur because of recurrence of the original liver disease, or graft complications including chronic rejection, hepatic vein stenosis, or small for size syndrome. The clinical presentation of transplant patients who develop portal hypertension is similar to those with native livers, and includes ascites and variceal bleeding.[33] Ultimately, TIPS is performed on 1 to 4% of liver transplant recipients.[34–36] In addition to the anatomic challenges that may be present due to the transplant anastomoses, the clinical efficacy and selection criteria differ compared with native livers. A meta-analysis of 13 studies showed that efficacy of TIPS after transplantation for the control of ascites was only 57%, compared with historical averages in native livers of 70 to 90%.[37] Additionally, studies have demonstrated that TIPS placement in posttransplant patients with MELD greater than 15 is associated with significantly higher mortality and increased risk of hepatic decompensation requiring repeat transplantation.[33,34,38] These studies show that while transplant patients with recurrent ascites may benefit from TIPS, their use should be limited to those with lower MELD scores and better hepatic reserve.

Conclusion

Ascites is the most common clinical manifestation of portal hypertension and contributes to morbidity and mortality in cirrhotic patients. TIPS is a well-validated therapy for refractory ascites and is superior at reducing the accumulation of fluid compared with paracentesis. More recent evidence has shown that TIPS also provides an improved TFS compared with LVP. To maximize the clinical efficacy and survival advantage, proper patient selection is crucial. Initial studies concluded that elective TIPS for ascites should be performed only in patients with MELD $\leq$ 18, which is reflected in current guidelines. However, more recent literature suggests that elective TIPS can effectively control ascites and potentially provide a survival advantage in patients with higher MELD scores ($\leq$ 24). The evolution of these findings likely represents the combination of improved medical management of cirrhotic patients, improved devices (covered stents vs. bare metal), and a better knowledge of selection criteria for potential TIPS patients.

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