Outcomes of TIPS for Treatment of Gastroesophageal Variceal Hemorrhage

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Abstract

Keywords

- ▶ transjugular intrahepatic portosystemic shunt
- ▶ gastroesophageal varices
- ▶ hemorrhage
- ▶ embolotherapy
- ▶ interventional radiology

Variceal hemorrhage is a life-threatening complication of cirrhosis that requires a multidisciplinary approach to management. The transjugular intrahepatic portosystemic shunt (TIPS) procedure is a minimally invasive image-guided intervention used for secondary prevention of bleeding and as salvage therapy in acute hemorrhage. This review focuses on the role of TIPS in the setting of variceal hemorrhage, with emphasis on the pathophysiology and conventional management of variceal hemorrhage, current and emerging indications for TIPS creation, TIPS clinical outcomes, and the role of adjuvant embolotherapy.

Objectives: Upon completion of this article, the reader will be able to describe variceal pathophysiology and conventional management, discuss current and emerging transjugular intrahepatic portosystemic shunt (TIPS) indications, identify TIPS clinical outcomes, and explain the role of adjuvant embolotherapy.

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Variceal hemorrhage is a catastrophic consequence of portal hypertension and a leading cause of death among cirrhotic patients. Management of this condition requires a

multidisciplinary approach that emphasizes early detection and encompasses pharmacologic, endoscopic, surgical, and image-guided interventional therapies. This review focuses on the role of the transjugular intrahepatic portosystemic shunt (TIPS) procedure in the context of variceal hemorrhage, with emphasis on variceal pathophysiology and conventional management, current and emerging TIPS indications, TIPS clinical outcomes, and the role of adjuvant embolotherapy.

Variceal Hemorrhage

Pathophysiology and Epidemiology

The hyperdynamic circulation and portal venous congestion attendant to longstanding liver cirrhosis contribute to the formation of esophageal and gastric varices, particularly in the presence of a hepatic venous pressure gradient exceeding 10 mm Hg.¹ Roughly 30 to 40% of compensated cirrhotic patients and 60% of decompensated cirrhotic patients present with esophageal varices at the time of diagnosis.² Gastric varices are less common, occurring in roughly 20% of patients with portal hypertension, but are associated with more

severe bleeding and mortality rates (approximating 25% at 2 years).^{3,4} Variceal enlargement is related to the severity and progression of the underlying liver disease.² The risk of hemorrhage is closely associated with vessel caliber—the yearly incidence is 5% in the presence of small vessels and up to 15% with medium or large varices.⁵ Overall, mortality following a bleeding episode ranges from 15 to 20%—or even higher—at 6 weeks, and approximately 60 to 70% of patients experience recurrent hemorrhage within 1 year of the initial episode.^{6,7}

Diagnosis and Management

The dismal prognosis associated with variceal hemorrhage highlights the importance of prompt diagnosis and treatment. All newly diagnosed cirrhotic patients undergo endoscopic evaluation and initiation of interval screening or prophylactic treatment as appropriate.⁸ Varices are classified by enteral location (esophageal, gastroesophageal, isolated gastric), anatomic position (fundus, greater curvature, lesser curvature), size (small, enlarged, large), configuration (straight, tortuous, coil shaped), and luminal occupation (less than one-third, greater than one-third).⁹ Primary prophylaxis is initiated in patients with large varices, those with small varices and advanced liver disease, and those with varices demonstrating signs of bleeding on endoscopy (such as nonpulsatile spurting, oozing, adherent clot, or a red wale sign).¹⁰ Nonselective β -blockers have been shown to slow progression of variceal size, reduce the risk of hemorrhage, and improve mortality^{11,12}; the use of carvedilol—a nonselective β -blocker with anti- α adrenergic properties—is the subject of ongoing investigation.¹³ Endoscopic treatment, such as band ligation, is an effective option for patients with medium to large varices in whom pharmacologic therapy is contraindicated or poorly tolerated.¹³

Acute variceal hemorrhage requires aggressive intervention. Initial management calls for basic fluid and blood product resuscitation, hemodynamic stabilization, and antibiotic prophylaxis; endoscopic treatments such as band ligation or sclerotherapy are used in conjunction with vasoactive agents to achieve and maintain hemostasis, with use of balloon tamponade (via a Sengstaken–Blakemore tube) reserved as a temporizing measure in extreme cases.¹⁴ These techniques are unsuccessful in 10 to 20% of cases, calling for rescue therapy in the form of emergent TIPS or surgical portocaval shunt creation.¹⁵ TIPS is typically preferred over surgery (particularly in patients with poor liver function), as operative mortality may be high in cirrhotic patients, although acute emergent variceal hemorrhage may be associated with significant mortality irrespective of treatment modality.^{16,17}

Established and Emerging Indications for TIPS in Variceal Hemorrhage

Current indications for TIPS creation in the context of gastroesophageal varices include the prevention of recurrent variceal hemorrhage in patients who demonstrate intolerance or resistance to medical and endoscopic treatment¹⁸; TIPS is not advocated, however, for prevention of rebleeding in patients

who have bled only once from esophageal varices.¹⁸ TIPS is also recommended as rescue therapy in cases of refractory acute bleeding,¹⁸ although recent data support a broader role for TIPS as first-line treatment for acute hemorrhage.^{19,20} At present, TIPS is not advised to prevent hemorrhage from varices that have never bled, to prevent bleeding from gastric antral vascular ectasia, and as primary therapy for portal hypertensive gastropathy.¹⁸

Patient Selection and TIPS Technical Considerations

With regard to patient selection, the Model for End-Stage Liver Disease (MELD) score is the preeminent risk stratification system for prediction of TIPS mortality outcomes.^{21–25} This objective, statistically founded, and liver-specific metric is based on serum bilirubin level, international normalized ratio, and creatinine laboratory values, and MELD scores performed at the time of TIPS creation are associated with high predictive capacity for early patient mortality, with c-statistics for variceal hemorrhage patients approximating 0.9 or greater at 1- and 3-month postprocedure.²⁵ Although the MELD system would routinely deem patients with higher scores to be poor TIPS candidates (scores exceeding 18 and 25 herald moderately and markedly increased short-term mortality risk, respectively), such selection criteria cannot be considered in isolation in cases of acute life-threatening variceal hemorrhage. In emergent scenarios, markedly decompensated liver disease should not blindly preclude application of a potentially lifesaving intervention, although the decisions for TIPS need be made on a case-by-case basis, accounting for the patient's best interest and after comprehensive discussion of the procedure benefits, risks, alternatives, and expected outcomes with the patient (if possible), family, and consulting physicians. Moreover, such cases should be primed for possible liver transplantation should this need arise. Alternatively, other approaches to variceal eradication, such as balloon retrograde transvenous obliteration for gastric varices,²⁶ may be considered in such high-risk cases, as this procedure does not involve portosystemic shunting, maintains native portal blood venous flow, and averts risk for worsening liver insufficiency (although it may worsen portal hypertension and associated sequela of ascites²⁷).

At the time of TIPS creation, the preferred degree of portosystemic pressure gradient reduction is less than 12 mm Hg for patients with variceal hemorrhage, as this threshold demarcates a significantly reduced risk for bleeding²⁸; a lower gradient may be required in the setting of gastric varices.¹⁸ Gastroesophageal variceal embolization at the time of TIPS creation is typically performed at the discretion of the primary interventional radiology operator, based on the clinical circumstance (presence of active bleeding), degree of portosystemic pressure gradient reduction after TIPS, size and number of varices, and the presence and amount of variceal filling following TIPS creation. Embolization may be performed before or following shunt creation. Pre-TIPS embolization has advantages of increased variceal filling and visualization as well as decreased risk of systemic

coil migration due to shunt absence, while post-TIPS embolization has the benefit of assessment for variceal decompression following TIPS, which could theoretically obviate need for closure of esophageal varices (although the authors believe that gastric varices should be uniformly embolized—see below). Embolic devices include 0.035- or 0.018-inch metallic coils or metallic vascular plugs, which require varix selection with a guiding catheter or sheath; sclerosing agents may also be considered. When pursuing embolization, care should be taken to perform thorough splenoportography to not only identify left gastric (coronary) vein varices (►Fig. 1A) (which usually feed esophageal varices), but also detect significant posterior gastric (►Fig. 1B) or short gastric varices (►Fig. 1C). Other veins of interest include the right gastric vein as well as the right and left gastroepiploic veins. Esophageal varices should prompt left gastric vein embolization, while gastric varices may require trapping through coil occlusion of the left gastric, posterior gastric, short gastric—and possibly other—veins with or without additional concurrent treatment (such as sclerotherapy).

Clinical Outcomes of TIPS for Variceal Hemorrhage

Secondary Prevention of Esophageal Variceal Hemorrhage

The prevention of recurrent hemorrhage in patients who survive an initial variceal bleed is critical given the high mortality associated with each bleeding episode. TIPS compares favorably to pharmacologic and endoscopic therapies, achieving similar mortality outcomes and rebleeding rates as low as 6% at 2 years.²⁹ TIPS creation is associated with a high rate of technical and clinical success; successful creation occurs in nearly 100% of cases, while immediate bleeding cessation is achieved in 90 to 100%.^{30,31} Current guidelines, however, favor TIPS as salvage therapy for patients who fail conventional treatment due to the absence of survival benefit and nontrivial risk of TIPS-related hepatic encephalopathy.¹⁸ Data comparing TIPS and surgical shunt creation are limited by highly selected patient cohorts that are not representative of most variceal bleeders and are confounded by the use of obsolete bare metal stent technology during TIPS creation.^{32–34}

Rescue Therapy for Acute Esophageal Variceal Hemorrhage

TIPS creation is employed as rescue therapy in the 10 to 20% of patients in whom acute variceal bleeding proves refractory to endoscopic and pharmacologic measures.¹⁴ As with TIPS created for secondary bleeding prevention, technical and clinical efficacy rates are high (each exceeding 90%), while 1-month rebleeding rates in the era of covered stent grafts are 10% or less.³¹ Mortality in this setting, however, may be as high as 36% at 6 weeks,¹⁸ a figure that is likely indicative of the severity of hepatic decompensation seen in this patient population given that the need for emergency TIPS is itself an independent predictor of mortality.³⁵ Cumulative (long-term) recurrent hemorrhage rates may approximate 20 to 30%.^{31,32,36–39}

Figure 1 (A–C) Digital subtraction portal venograms performed before TIPS creation in three different patients reveal large (A) left gastric (coronary) vein varix (arrowheads), (B) posterior gastric vein varix (arrowheads), and (C) short gastric vein varix (arrowheads). TIPS, transjugular intrahepatic portosystemic shunt.

There are few studies comparing TIPS and emergency surgical portocaval shunts in the treatment of acute variceal hemorrhage. In 2012, Orloff et al reported results of a randomized controlled trial comparing TIPS and emergency surgical portocaval shunt creation in the treatment of acute variceal hemorrhage.¹⁷ A total of 154 consecutive patients with cirrhosis and acute bleeding esophageal varices were randomly assigned to undergo TIPS or surgical portocaval shunt within 24 hours of presentation. While surgical portocaval shunts were deemed more effective than TIPS in controlling bleeding within (100 vs. 80%) and after (97 vs. 22%) 30 days, TIPS were exclusively created using bare metal stents, which are associated with higher rates of shunt dysfunction.^{40,41} This outdated technology has been predominantly supplanted in clinical practice by expanded polytetrafluoroethylene (e-PTFE) covered stent grafts, which are associated with improved patency and a lower rate of shunt dysfunction.^{30,42} These results are therefore not generalizable, as the relative efficacy of surgical portocaval shunts must be measured against the current standard of care.

Early (Nonsalvage) TIPS Creation in Acute Hemorrhage

Recent investigation into expanding the role of TIPS in treating variceal hemorrhage has yielded promising results. In 2012, Garcia-Pagan and colleagues reported the outcome of a multicenter trial comprising 63 patients with acute variceal hemorrhage who were at high risk for treatment failure, defined as those with Child–Pugh class B or Child–Pugh class C (score less than 14) disease and active bleeding.¹⁹ Patients were initially treated with standard pharmacologic and endoscopic treatment; a total 32 patients were then randomly assigned to undergo covered stent graft TIPS creation within 72 hours of presentation, while the control group continued pharmacologic and endoscopic treatment. Early TIPS was more successful in controlling bleeding (97 vs. 55%) and was associated with a significant increase in 6-week survival (97 vs. 61%).¹⁹ Although this study was limited by a highly selected patient cohort and a small sample size, the results were validated in a larger retrospective surveillance study in which the early TIPS and control groups consisted of 45 and 30 patients, respectively.²⁰ Again, early TIPS compared favorably to standard therapy with regard to the 1-year actuarial probability of bleeding control (93 vs. 53%) and survival (86 vs. 70%). Larger prospective series are required to confirm these results and potentially identify other patient groups that would benefit from early intervention.

Gastric Varices

Data regarding the treatment of gastric varices are limited. Initial management resembles that of esophageal variceal bleeding, with endoscopic delivery of n-butyl-2-cyanoacrylate employed as the first-line method of hemostasis.^{43,44} TIPS creation is also highly effective in this setting, achieving control of initial bleeding in 90% of cases with rebleeding rates as low as 15%.^{45–47} While rebleeding is much lower in patients undergoing TIPS compared with cyanoacrylate, they have similar efficacy in obtaining initial hemostasis, and have comparable morbidity and mortality.⁴⁶ However, the higher

cost and increased incidence of encephalopathy attendant to TIPS creation have relegated it to use as a second-line therapy behind endoscopic cyanoacrylate glue injection.⁴⁷

Adjunctive Embolotherapy

The role of adjunctive embolotherapy at the time of TIPS creation is a matter of contention. In theory, embolic occlusion will limit filling or recanalization of varices and reduce the incidence of recurrent hemorrhage due to shunt dysfunction⁴⁸; moreover, closure of collateral channels consolidates flow through the intrahepatic shunt. However, because contemporary e-PTFE covered stent grafts are associated with superior patency and a markedly decreased incidence of shunt dysfunction (less than 10%) compared with their bare metal precursors, reducing the likelihood for variceal recanalization, the need for routine embolization is now called into question.^{30,49} Additionally, embolotherapy increases procedure duration, cost, and radiation exposure, and is associated with a low incidence of postembolization syndrome when sclerosant agents are used, which may prolong hospital stay and further increase expense.⁵⁰ While the benefits of embolization may be limited to certain subsets of patients, such as those with continued variceal filling despite a patent shunt, those with submucosal or large caliber vessels, and those with gastric varices,^{51,52} data supporting embolization are growing.

Tesdal et al reported that patients who underwent bare metal TIPS and concurrent embolotherapy had significantly lower rebleeding rates at 2 and 4 years compared with those undergoing TIPS alone (16 vs. 39% and 19 vs. 47%, respectively) while also experiencing a longer temporal interval between the recurrence of portal hypertension and subsequent rebleeding.⁵⁰ A retrospective series comparing embolotherapy versus no embolization during covered stent graft TIPS creation in 52 patients found a trend toward increased rebleeding in the nonembolization cohort,⁵² and a recent prospective randomized controlled trial of TIPS alone versus TIPS with concurrent coronary vein embolization found a significant reduction in 6-month overall rebleeding rate (5.7 vs. 20%) favoring the embolization group.⁵³ The efficacy of embolotherapy was recently evaluated in a meta-analysis by Qi et al.⁵⁴ Six studies were included, in which both bare metal and covered stents were used. The authors found that adjunctive embolotherapy was associated with a significantly lower rate of rebleeding; however, no significant differences were identified with respect to the incidence of shunt dysfunction, encephalopathy, or mortality. Continued investigation in larger prospective studies using covered stent grafts will define the precise role of embolotherapy and may elucidate the optimal embolic agents and techniques.

Conclusion and Future Directions

The TIPS procedure plays an important role in the contemporary management of variceal hemorrhage. It is supported by robust evidence as secondary prevention of bleeding and as salvage therapy in acute hemorrhage. The data supporting early TIPS creation in high-risk patients are promising,

though limited, and the role of adjuvant embolotherapy remains controversial. Future investigation may yield further insight into the utility of early TIPS creation and reveal other patient populations that might benefit from this intervention.

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