Pre-emptive TIPSS in Acute Variceal Bleeding: Current Status, Controversies, and Future Directions

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Introduction

Acute variceal bleeding (AVB) is associated with significant short-term morbidity and mortality. Pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPSS) is recommended to prevent rebleeding in AVB patients with a high risk of rebleeding. Despite the benefit of preventing rebleeding and de-novo ascites, the uptake of p-TIPSS remains low because of logistic challenges in the real-world setting. In this review, we summarize the current evidence and controversies on p-TIPSS including patient selection for p-TIPSS, particularly in the setting of NASH cirrhosis and acute-on-chronic liver failure, the role of sarcopenia, renal impairment in the setting of p-TIPSS. Finally, we summarize both pharmacological and nonpharmacological strategies to optimize outcomes in patients undergoing p-TIPSS.

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Abstract

Acute variceal bleeding (AVB) is associated with significant short-term morbidity and mortality. Pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPSS) is recommended to prevent rebleeding in AVB patients with a high risk of rebleeding. Despite the benefit of preventing rebleeding and de-novo ascites, the uptake of p-TIPSS remains low because of logistic challenges in the real-world setting. In this review, we summarize the current evidence and controversies on p-TIPSS including patient selection for p-TIPSS, particularly in the setting of NASH cirrhosis and acute-on-chronic liver failure, the role of sarcopenia, renal impairment in the setting of p-TIPSS. Finally, we summarize both pharmacological and nonpharmacological strategies to optimize outcomes in patients undergoing p-TIPSS.

Keywords: Transjugular intrahepatic portosystemic shunt; Hemorrhage; Portal hypertension; Cirrhosis.

Pre-emptive TIPSS: current status

A landmark study by Garcia-Pagan et al. was pivotal in redefining the role of p-TIPSS in the management of AVB. Using simple clinical scores to identify Child-Turcotte-Pugh (CTP) class C or CP-B patients with active bleeding during endoscopy and with a high risk of rebleeding, early placement of TIPSS within 72 hour successfully prevented rebleeding and decreased mortality in these patients. The benefits of p-TIPSS go beyond preventing rebleeding to preventing mortality and de-novo ascites, without signifi-
cantly increasing the risk of hepatic encephalopathy. The benefits of early p-TIPSS were also described in an RCT by Lv et al., independent of active bleeding during endoscopy. In contrast, the survival benefit of p-TIPSS was not observed in an RCT by Dunne et al., yet a higher risk of hepatic encephalopathy following p-TIPSS was observed. Unfortunately, the survival benefit was inconclusive because this study was underpowered because of slow recruitment. To reconcile the controversies on the survival benefit of p-TIPSS, a recent meta-analysis and trial sequential analysis showed that the evidence from current RCTs is insufficient to support a 6-week survival benefit with p-TIPSS compared with the standard of care. A summary of all RCTs evaluating p-TIPSS is shown in Table 1.

Pre-emptive TIPSS: ongoing controversies

Ongoing controversies in defining the optimal role of p-TIPSS include patient selection, particularly in NASH cirrhosis patients with associated cardiovascular risk factors and in patients with acute-on-chronic liver failure, and the role of sarcopenia and renal impairment in the setting of p-TIPSS.

**Patient selection**

There are conflicting views on whether patients with Child-Pugh-Turcotte (CPT) class B disease and active bleeding or with MELD scores between 12 and 18 would benefit from pre-emptive TIPSS. Whether p-TIPSS remains beneficial when performed after 72 hours is debatable, because real-world evidence suggests that benefits may be observed in patients who underwent TIPSS after 72 hours of AVB. While active bleeding was defined as the presence of active bleeding during the insertion of endoscope, the reliability of the finding is also subject to the time that endoscopy was performed. The finding of active bleeding was associated with an increased risk of death among CTP class B patients in some studies, but not in others. Patient selection for pre-emptive TIPSS using the CTP score may be limited by subjective variables within the CTP score as it does not distinguish between the individual phenotype of liver dysfunction (liver synthetic dysfunction versus portal hypertension-related). Moreover, data on the efficacy of pre-emptive TIPSS in preventing rebleeding and death with gastric variceal bleeding is also scarce. A multicenter trial (GAVAPROSEC) is currently underway to compare the benefit of pre-emptive TIPSS and glue obliteration in preventing rebleeding and death in bleeding gastric varices. Lastly, the survival benefit of p-TIPSS was recently questioned because the standard of care (carvedilol, variceal band ligation, and early access to endoscopy) has improved since the landmark trial conducted a decade ago. A large multicenter randomized trial (REACT-AVB) comparing p-TIPSS with the standard of care in patients with Child-Turcotte-Pugh scores 7–13 is underway in the United Kingdom. The trial will address fundamental questions on the survival benefits and the ideal target population for p-TIPSS in cirrhosis patients with AVB.

**Pre-emptive TIPSS in NASH-related cirrhosis**

Given the rising obesity pandemic, NASH cirrhosis will likely emerge as the driving cause of cirrhosis. However, the impact of p-TIPSS on NASH cirrhosis is not clear, as NASH-related cirrhosis has been underrepresented in all the existing trials, in which the primary etiologies were alcoholic cirrhosis and chronic hepatitis B. There are several considerations when selecting NASH cirrhosis patients with AVB for p-TIPSS. First, cardiovascular complications, a key exclusion criterion for TIPSS, are prevalent in NASH cirrhosis. Cardiac evaluation is paramount because p-TIPSS may potentially unmask undiagnosed cardiovascular disease. TIPSS insertion shunts a significant volume of blood from the splanchnic into the systemic circulation, with consequential increases in cardiac output and right heart pressure. While the sudden rise in right heart pressure following TIPSS is usually transient, the development of cardiac decompensation following TIPSS can be detrimental. Patients with severe left ventricular dysfunction, severe acute coronary disease, or severe pulmonary hypertension should not proceed with p-TIPSS. Current guidelines recommend a 12-lead electrocardiogram and N-Terminal pro-B-type natriuretic peptide before TIPSS insertion. The fact that NASH cirrhosis patients experience portal hypertension-related at a lower HVPG may affect patient selection for p-TIPSS using HVPG. That is further confounded by the inter-observer variability of HVPG, particularly in cases with decompensated NASH cirrhosis. In summary, TIPSS can be associated with an increased risk of HE and liver dysfunction in NASH-related cirrhosis. Therefore, insertion of p-TIPSS in NASH cirrhosis patients must consider co-existing cardiac and renal comorbidities to minimize potential TIPSS-related complications in those patients.

**Acute-on-chronic liver failure**

Acute-on-chronic liver failure (ACLF) is a clinical syndrome associated with multiorgan failure and high short-term mortality. Because the hemodynamic changes following TIPSS insertion may precipitate cardiac and liver failure, application of p-TIPSS in the setting of ACLF must be supported by strong evidence. In a multicenter prospective cohort study of 2,138 patients with AVB, the presence of ACLF retrospectively defined following European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) consortium criteria predicted mortality in patients with AVB. Among 380 patients (17.8%) who had ACLF, p-TIPSS was associated with a decreased risk of 6-week rebleeding (hazard ratio: 0.128; 95% confidence interval: 0.017–0.937; p = 0.043), 42-day mortality (13.6% vs. 51.0%, p = 0.002 and 1-year mortality (22.7% vs. 56.5%, p = 0.002). However, before confirming the survival benefit of p-TIPSS in the setting of ACLF, there are several key considerations. First, the benefit of p-TIPSS was derived from only 22 ACLF patients (5.6% of the overall ACLF cohort), which raises concerns of the generalizability of the findings. Second, observational studies are subject to selection and indication bias. Subjects who underwent p-TIPSS had lower baseline MELD scores and less severe ACLF grade than those who did not undergo p-TIPSS. Third, there are differences in the definition, clinical phenotype, and primary etiology of ACLF between different ACLF consortia, which complicates patient selection for p-TIPSS in this setting. Between ACLF subjects with or without p-TIPSS, it is important to know the proportions of ACLF patients with intrinsic liver failure and with ongoing sepsis that may deter consideration of p-TIPSS. While p-TIPSS can reduce rebleeding, is it sufficient to change the trajectory of ACLF that results in a survival benefit in ACLF? Given the relative paucity of data, randomized trials are required to confirm the survival benefits on p-TIPSS in the setting of ACLF.

**Sarcopenia**

Sarcopenia is present in 40% of patients with decompensi-
| Author                  | Patient characteristics | No. of patients (TIPSS vs. control) | Type of stent               | Standard of care                                      | Main findings                                                                 | HE (%) | TIPSS vs. control |
|-------------------------|-------------------------|-------------------------------------|-----------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------|--------|-------------------|
| Jalan et al. 1997        | Not defined             | ETOH                                | 31 vs. 27                   | Expandable uncovered stent                             | Variceal rebleeding frequency and severity reduced with TIPSS ($p<0.0006$). No significant difference in mortality rates or frequency of HE | 36%    | 33%               |
| Pomier-Layrargues et al. 2001 | CTP 7–12               | ETOH, cryptogenic                    | 41 vs. 39                   | EVL performed on days 1 and 10, then every 3–4 weeks until obliteration. 3-monthly surveillance thereafter | Variceal rebleeding significantly lower in TIPSS group at 2 years ($p<0.001$) but no difference in survival rate. No difference in probability of HE | 47%    | 44%               |
| Monescollo et al. 2004   | HVPG ≥ 20mmHg within 24hrs of AVB | ETOH, HCV                           | 26 vs. 26                   | Uncovered stent                                        | Sclerotherapy then NSBB, or EVL if NSBB contraindicated or not tolerated       | No difference in 6-week mortality. Reduction in in-hospital and 1-year mortality with TIPSS ($p=0.02$, $p=0.01$ respectively). No increase in de no HE with TIPSS | 31%    | 35%               |
| García-Pagán et al. 2010 | CTP C≤13 or CTP B with AVB | ETOH, HCV                           | 31 vs. 32                   | e-PTFE-covered stent                                   | Optimization of NSBB and ISMN. Second EVL within 7–14 days then every 10–14 days until eradication | 6-week and 1-year survival higher in early TIPSS (NNT=3.3, NNT=4.0 respectively). Reduction in 1-year rebleeding ($p<0.001$). No difference in HE ($p=0.13$) | 25%    | 39%               |
| Lv et al. 2019           | CTP B or C<14           | HBV, HCV, ETOH                       | 86 vs. 46                   | e-PTFE-covered stent                                   | Optimization of NSBB. Second EVL within 7–14 days, then every 14 days until eradication | Transplant-free survival higher in TIPSS at 6-weeks and 1 year ($p=0.02$, $p=0.046$). No difference in HE ($p=1.00$) | 35%    | 36%               |
| Dunne et al. 2020        | CTP B and Cs<13         | ETOH                                | 29 vs. 29                   | e-PTFE-covered stent                                   | Optimization of NSBB. Endoscopy at 2- to 4-week intervals until variceal eradication | No difference in 6-week or 1-year survival with early TIPSS. Trend toward reduced rebleeding with TIPSS ($p=0.09$). HE more common with TIPSS ($p=0.04$) | 41%    | 17%               |

AVB, acute variceal bleeding; CTP, Child-Turcotte-Pugh; ETOH, alcohol; EVL, endoscopic variceal ligation; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; NNT, number needed to treat; NSBB, Nonselective beta-blocker; TIPSS, transjugular intrahepatic portosystemic shunt.
sated cirrhosis and has been associated with an increased risk of hepatic encephalopathy and death in cirrhosis patients. Sarcopenia has been associated with an increased risk of HE following TIPSS, and this association was not consistently demonstrated. On the other hand, TIPSS was associated with an improvement in sarcopenia. Retrospective analysis of 27 patients showed that the skeletal muscle index improved 6 months following TIPSS insertion. Current guidelines recommend sarcopenia assessment before TIPSS insertion, but sarcopenia should not be considered as contraindication for p-TIPSS. Further studies are required to understand the role of sarcopenia in patient selection for p-TIPSS.

Renal impairment

Most studies on p-TIPSS excluded patients with severe renal impairment because TIPSS was associated with a higher risk of hepatic encephalopathy and a lower natriuretic effect in these patients. The presence of acute kidney injury in the setting of AVB is generally not considered a contraindication for p-TIPSS. Among advanced cirrhosis patients with hepatorenal syndrome, TIPSS placement was associated with improvement in renal function, but a significantly higher risk of HE following TIPSS. Moreover, a recent meta-analysis highlighted significant heterogeneity among the included studies and the lack of high-quality studies evaluating TIPSS in patients with hepatorenal syndrome. Due to the increased risk of HE, p-TIPSS in the setting of AVB with hepatorenal syndrome or severe chronic renal impairment is currently considered experimental.

Post-TIPSS hepatic encephalopathy

HE is generally considered a relative contraindication in the setting of rescue TIPSS, as the risk of HE is outweighed by the survival benefit of TIPSS as a life-saving procedure. However, the concern of HE is reasonable in stable patients undergoing TIPSS as a life-saving procedure. Overall, the survival benefit of TIPSS is demonstrated in an observational study by Leng et al. which showed that rifaximin did not reduce post-TIPSS HE. The urgency to perform p-TIPSS within 72 hour of AVB may influence the adoption of rifaximin as primary prophylaxis for HE following p-TIPSS. Currently, a European multicenter RCT (the PEARL trial) of combined treatment with rifaximin and lactulose for HE prophylaxis is currently ongoing. The results are highly anticipated.

The existence and diameter of the portosystemic shunt (SPSS) is an independent predictor of post-TIPSS hepatic encephalopathy. A recent randomized trial by Lv et al. reported a lower risk of HE following TIPSS with concurrent embolization of a large spontaneous portosystemic shunt in patients undergoing TIPSS. Following embolization of large collaterals, the amount of blood shunting through TIPSS was reduced, as it was limited by the diameter of the TIPSS, which is often smaller than the co-existing large SPSS. The benefit of embolization of SPSS during TIPSS was demonstrated in an observational study by Leng et al. in which the risk of HE was similar in patients who underwent SPSS embolization and in those without SPSS. It makes sense that the risk of HE was decreased by creating a new, smaller portosystemic shunt, further randomized trials are needed to confirm safety from the perspective of variceal bleeding and ascites management. Meanwhile, a fully covered, small-diameter controlled-expansion stent can be used to use to minimize the risk of HE following p-TIPSS. Meanwhile, a smaller 8 mm covered stent can be considered as it has been shown equally effective in preventing rebleeding while reducing the risk of post-TIPSS HE by 47% compared with a 10 mm stent. Special attention should be paid to patients with sarcopenia, diabetes mellitus, or renal impairment, in whom the risk of HE is inherently greater. Patients should maintain sufficient caloric intake of 35–40 kcal/kg/body weight/day and a protein intake of 1.2–1.5 g/kg/body weight/day. Prolonged fasting should be avoided whenever possible. Finally, to reduce the risk of renal impairment, nephrotoxic drugs should be stopped before p-TIPSS, and the amount of iodinated contrast used during TIPSS should be minimized with the help of endovascular ultrasound and carbon dioxide venography.

Conclusions

In summary, p-TIPSS is an important tool to reduce rebleeding in cirrhosis patients with AVB. While the benefits of reducing rebleeding and de-novo ascites are evident, controversies remain concerning patient selection, particularly among those with NASH cirrhosis and acute-on-chronic liver failure. Hepatologists must be familiar with the strength and limitations of p-TIPSS and be aware of the strategies to optimize outcomes in patients undergoing p-TIPSS. Future work should focus on improving access to p-TIPSS and individualizing p-TIPSS in the setting of AVB.
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