Grand Rounds

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Emergency TIPS in a Child-Pugh B patient: When does the window of opportunity open and close?

Jonel Trebicka*

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Summary

Transjugular intrahepatic portosystemic shunt (TIPS) is used to treat complications of cirrhosis such as variceal bleeding and refractory ascites, but it also bears the risk of liver failure, overt hepatic encephalopathy (HE) and cardiac decompensation. Variceal bleeding may be controlled using endoscopic and medical treatment in patients with compensated cirrhosis; in decompensated patients, however, TIPS improves survival. Therefore, an early TIPS (within 72 h or if later, still early after bleeding) might improve the survival of patients by preventing an inflammatory response and bacterial translocation. Both these processes mediate an impaired immunological and hemodynamic response, thereby facilitating the development of acute-on-chronic liver failure (ACLF) and/or death. Similarly, in patients with refractory ascites, TIPS should be used early in treatment to prevent acute kidney injury (AKI) and hepatorenal syndrome (HRS) after precipitating events induced by complications of portal hypertension. Whether TIPS and/or embolization should be used to treat portal vein thrombosis and spontaneous shunts is still a matter of debate and should be further investigated.

In summary, the careful selection of patients for TIPS is crucial. New biomarkers, especially those evaluating systemic inflammation and bacterial translocation, might improve the predictive value of established clinical parameters such as bilirubin and overt HE. However, a significant amount of further research must be carried out.

Clinical vignette

Department of Internal Medicine I, University of Bonn, Bonn, Germany; Institute of Clinical Research, Odense University Hospital, University of Southern Denmark, Odense, Denmark

This case describes a 68-year old Caucasian male patient with known alcoholic liver cirrhosis (Child-Pugh B 8 points; model for end-stage liver disease [MELD] score 10, MELD sodium [$MELD_{Na}$] 13). The patient presented with hematemesis, systolic blood pressure of 65 mmHg, hemoglobin (Hb) levels of 3.6 mg/dl, bilirubin of 2.2 mg/dl, albumin of 3.0 g/dl, sodium 136 mval/L, creatinine 0.6 mg/dl, white blood count of 9.2 g/L and an international normalized ratio (INR) of 1.1. After excessive vomiting and suspected aspiration, the airways were protected by endotracheal intubation. The patient received intravenous antibiotics (piperacillin/tazobactam), terlipressin and was admitted to the Intensive Care unit (ICU) for further management and mechanical ventilation. The emergency endoscopy identified signs of recent bleeding from a ruptured oesophageal varix. The varix was ligated and the endoscopy revealed further five grade III varices with red color signs. Hereafter, the patient received red cell transfusions. Terlipressin and antibiotics were continued and spontaneous bacterial peritonitis could be excluded by means of diagnostic paracentesis of the mild ascites. The day after, the patient was successfully extubated, presenting with a Hb of 9 mg/dl and C-reactive protein of 35 mg/dl.

On day three, his Hb levels slowly declined to 6 mg/dl, and a control endoscopy identified a previous ligation ulcer generating a oozing bleeding. When repeated attempts to ligate or place tissue glue at the bleeding site failed, a self-expandable, esophageal metal stent was placed, concealing the defect. Doppler-ultrasound detected an adherent hypoechoic thrombus in the main trunk of the portal vein with very slow flow (10 cm/s), leading us to suspect a recent partial portal vein thrombosis (PVT). Echocardiography excluded right heart insufficiency and pulmonary arterial hypertension. On day four, the patient was subject to an emergency transjugular intrahepatic portosystemic shunt (TIPS) with embolization of the varices and all visible spontaneous shunts. The esophageal stent was extracted three days after TIPS. The patient was

* Corresponding author. Address: Department of Internal Medicine I, University of Bonn, Sigmund-Freud Str. 25, D-53105 Bonn, Germany. Tel.: +49 228 287 15507; fax: +49 228 287 19718.
E-mail address: jonel.trebicka@ukb.uni-bonn.de.

discharged from the ICU four days after TIPS intervention and was discharged from the hospital a further four days later. During regular check-ups at the out-patient clinic, which were conducted six weeks and two months after TIPS, the patient presented without ascites or HE, but with a MELD score of 10 and Child-Pugh score B (7 points).

Despite the positive short-term outcome, this clinical case raises several frequently debated questions, which might reflect the differences in workflow in different countries, expertise of hospitals and responsibilities of disciplines:

- Is active bleeding during endoscopy still a prevailing high-risk criterion for early TIPS in patients despite the use of potent vasoconstrictors such as terlipressin?
- Should PVT limit TIPS use or, on the contrary, should it be an indication for TIPS?
- Is just the TIPS-shunt implantation sufficient, or should embolization of the collaterals always be part of TIPS insertion, especially regarding gastric varices and HE?
- What investigations should be included in the work-up before TIPS insertion and during the follow-up, and should TIPS be performed in every hospital with an emergency endoscopy unit?

This grand round paper will try to elaborate on these questions while describing the pathophysiology, diagnostic and prognostic biomarkers, current management, areas of uncertainty and discussing beyond the guidelines.

Pathophysiology

General pathophysiology of portal hypertension

Portal hypertension in cirrhosis is the consequence of an increased resistance to portal venous blood flow [1]. While increased hepatic resistance is the starting point of portal hypertension in cirrhosis, the extrahepatic vascular changes induced by portal hypertension are the major driving forces behind complications [1,2]. Vascular dysfunction, characterized by hypocontractility in splanchnic and systemic vessels, leads to splanchnic vasodilation with a consequential drop in effective arterial blood volume [2]. Subsequently, the systems involved in vasoconstriction, such as the renin-angiotensin-system (RAS) and the sympathetic system, become activated [2,3]. However, they fail to increase the resistance in extrahepatic vessels, as the intracellular signaling pathways are defective due to deactivation of RhoA/Rho-kinase and overexpression of beta-arrestin2. Conflictingly, the upregulation of RAS and catecholamines aggravate portal hypertension further as they enhance profibrotic conversion in the liver and hepatic vasocontraction [2–5]. The only remaining mechanism sufficient to rescue the systemic hemodynamic situation is an increase in cardiac output, which also leads to higher portal venous inflow due to splanchnic vasodilation, thereby further increasing portal pressure [6] (Fig. 1A).

The role of extrahepatic circulation and shunting

These circulatory changes impair renal perfusion, and subsequently decrease sodium excretion, facilitating ascites formation [6]. Ascites is a definitive sign of portal hypertension and decompensation, and an indicator for a higher overall morbidity and mortality [7]. Ascites predisposes patients to bacterial translocation [8,9] and thereby aggravates portal hypertension. This is indicated by a higher incidence of variceal bleeding in patients with bacterial translocation [10]. Bacterial translocation and infection, especially spontaneous bacterial peritonitis, accentuates hemodynamic dysfunction and induces renal failure (acute renal injury, hepatorenal syndrome), which is mainly attributed to encroachment on cardiac reserve in these patients [6,11,12] (Fig. 1B).

In portal hypertension, collateral formation, which decreases portal pressure and/or portal venous inflow is possible. Unfortunately, instead of improving the hemodynamic situation, collateral formation and/or opening of pre-existing portosystemic shunting veins, induces subsequent complications such as the formation and induction of variceal bleeding, hepatic encephalopathy (HE) and liver dysfunction [1,13,14].

Treatment of portal hypertension

To date, sufficient and effective treatment of portal hypertensive complications is limited to either the use of acutely potent splanchnic vasoconstrictors (e.g., terlipressin), the classical prevention of bleeding using non-selective beta-blockers (NSBB), or endoscopic therapy. NSBB, introduced 35 years ago by Lebrec *et al.* [15], lower cardiac output and increase splanchnic vascular tone, curtailing the portal venous inflow [16]. NSBB decrease portal pressure sufficiently to prevent variceal bleeding. In combination with endoscopic therapy, they also reduce re-bleeding and improve survival in patients with cirrhosis and varices, as well as patients with acute-on-chronic liver failure (ACLF) [17,18]. This being said, patients under primary or secondary prophylaxis with NSBB still experience bleeding and progression of liver disease. In almost half of patients, NSBB do not elicit the desired hemodynamic response and do not prevent early re-bleeding [19,20]. Furthermore, the use of NSBB in refractory ascites might have deleterious effects [21], probably due to the restriction in cardiac