Advances in the treatment of esophageal varices: assessing covered tips versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in patients with portal vein thrombosis

Rezwan Ahmed[1], Bashar AbuLeil[2], Yaser Rayyan[2]

[1]Department of Internal Medicine, Houston Methodist Hospital, Houston, TX, USA; [2]Department of Gastroenterology and Hepatology, Jordan University School of Medicine, Amman, Jordan

Correspondence to: Yaser Rayyan, MD, FACP, FASGE. Professor of Medicine, Jordan University, School of Medicine, Department of Gastroenterology and Hepatology, Jordan University Hospital, Amman, Jordan. Email: yasermhr@aol.com.

Provenance: This is a guest Editorial commissioned by Editor-in-Chief Xingshun Qi (Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang, China).

Comment on: Lv Y, Qi X, He C, *et al.* Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial. Gut 2017. [Epub ahead of print].

Received: 05 January 2018; Accepted: 10 January 2018; Published: 06 March 2018.

doi: 10.21037/amj.2018.01.10

View this article at: http://dx.doi.org/10.21037/amj.2018.01.10

Attempts to treat esophageal varices (EV) started as early as 1945 by Dr. Allen Whipple when he used surgical techniques to create an anastomosis between splenic and renal veins (1). Using surgical shunts to treat underlying portal hypertension and variceal bleeding continued on for several decades. In the 1950s, Sengstaken and Blakemore used a double-balloon tamponade technique in approaching bleeding EV (2). Terblanche *et a.l* pioneered sclerotherapy for management of varices in the late 1970s (3). In 1996 the multiband ligator was introduced by Saeed, who built upon previous models of single shooter bands (4). Transjugular intrahepatic portosystemic shunting (TIPS) was first successfully done in 1988 as an alternative to surgical options (5). Since then, the role of each component changed dramatically with improvement in technical expertise and the types of material used for the TIPS shunt creation.

Growing understanding of the pathophysiological, pharmacological and clinical aspects of management of esophageal variceal bleeding has allowed us to develop better treatment approaches. Secondary prophylaxis after an index variceal bleeding is the current standard of care for cirrhotic patients; this consist of endoscopic band ligation (EBL) with non-selective B blocker (NSBB) as the first line of treatment and covered TIPS for those who fail endoscopic therapy (6). Recently an early TIPS with polytetrafluoroethylene-covered stents within 72 hours was expanded to include patients bleeding from EV, gastroesophageal varices type 1 & 2 (GOV1 and GOV2), and for those patients who are at high risk of treatment failure after initial pharmacological and endoscopic therapy (e.g., Child-Pugh class C <14 points or Child-Pugh class B with active bleeding) (6,7).

Despite all these advances, secondary prophylactic treatment of EV in patients with portal vein thrombosis (PVT) in the setting of liver cirrhosis is still not well defined. These patients are treated with EBL and NSBB as in patients without PVT followed by anticoagulation after eradication of the varices or when it is felt to be safe by the treating physician. To address this issue Lv *et al.* sought to compare the standard of care against TIPS in patients with a history of variceal bleeding in the setting of PVT using an open-label randomized controlled study (8). For this particular study, 52 patients of Chinese descent with bleeding varices were randomized within a day after admission following control of bleeding with EBL and medical therapy to TIPS (8 mm expanded polytetrafluoroethylene-covered stents) *vs.* continued standard of care with EBL + drug therapy. Patients in

both arms of the study received anticoagulation [*TIPS*: urokinase pre-procedure in selected patients to assure TIPS flow and continued anticoagulation with warfarin] [*EBL + drug therapy*: eradication of varices with NSBB followed by anticoagulation with a goal therapeutic INR level of 2–3]. The patients were followed for an average of 30 months primarily for variceal rebleeding. Survival, overt hepatic encephalopathy (OHE), portal vein recanalization and rethrombosis, and other complications of portal hypertension served as secondary endpoints in the study.

During the follow-up period, rebleeding occurred in 5 patients (21%) in the TIPS group and 15 (60%) in EBL + drug group. Of those, 4 (17%) patients in the TIPS group and 13 (52%) patients in the EBL + drug, the bleeding was attributed to variceal bleeding. However, this did not translate into survival benefit between the 2 groups (67% *vs.* 84%; P=0.152). These findings are consistent with a previous study done two years earlier by Luo *et al.* (9). Previous other studies in cirrhotic patients without PVT with the same premise of examining TIPS vs EBL + drug also did not show any survival benefit (10-12). The failure to show any survival benefit may suggest that the status of the liver function as reflected by the MELD score is far more important predictor for survival than the determinant risk factors in the case of variceal-type bleeding. Even in the subgroup analysis in this study, the extension of the PVT to SV or SMV had no significant impact on survival. This is consistent with United Network for Organ Sharing (UNOS) data from 2002 to 2013 and another study on viral hepatitis-related cirrhosis where PVT was not associated with increased risk of death or reduced chance of undergoing liver transplantation (13,14). And while the benefit of anticoagulation on survival was demonstrated in one study, where anticoagulation (enoxaparin) improved the hepatic microcirculation and integrity of the vascular endothelium that subsequently reduced the risk of bacterial translocation with a resultant survival benefit, this was not demonstrated by Lv *et al* despite the EBL + drug group being on anticoagulation for a longer period of time; one possible explanation for this could be the difference in the drug choice of enoxaparin vs warfarin, another would be that the study was underpowered to detect such a difference (15).

As far as the secondary events, there was no significant difference between the two groups in terms of OHE, worsening ascites, hepatic hydrothorax or hepatorenal syndrome. This must be interpreted with caution given the small sample size in the Lv *et al.* study. The 12-month probability of OHE was 23% in the TIPS *vs.* 17% in the EBL + drug (P=0.434). Among patients who experienced OHE, the mean number of episodes was 2.2±1.3 in the TIPS group and 1.7±1.1 in the EBL + drug group, respectively (P=0.220). Similar probabilities were observed by Luo *et al* despite using a 10-mm covered stent vs an 8-mm stent (9).

The high recanalization rate of the portal vein in this setting—TIPS group achieved a complete or partial recanalization of the portal vein (95%) while only (70%) of the EBL + drug group- may have clinical implications in appropriate selection of patients for TIPS over the standard EBL + drug group. In patients with refractory ascites for example, patients waiting for liver transplantation where the PVT may or may not have a significant survival impact post transplantation, enhancing the patency of the PV may prevent the thrombus extension and allow for a more feasible end to end anastomosis especially in living donor liver transplantation (16).

Technical failure of TIPS insertion has improved significantly over the past 10 years and mainly is associated with extensive PVT. It may also compromise an intended liver transplant procedure if placed distally into the PV trunk and SMV. Polytetrafluoroethylene-covered stents have a lower rate of dysfunction (17). Furthermore, anticoagulation with careful monitoring in this study did not result in an increased risk of bleeding and may be of auxiliary benefit in this setting knowing that EBL + NSBB in patients with cirrhosis and PVT is associated with a delay in anticoagulation.

In addition, the role of thrombophilic genetic defects in the development of PVT in cirrhosis remains controversial with venous stasis and degree of liver dysfunction appears to be the most important risk factor for the development of PVT (18,19). Yong *et al.* demonstrated a very low prevalence of prothrombin G20210A and factor V Leiden gene mutations in Chinese patients with cirrhosis and PVT (20) and a high prevalence of methylenetetrahydrofolate reductase (MTHFR) *C677T* gene mutation which might be explained by ethnic differences. This was also demonstrated in other studies that showed the presence of these genetic mutations was not strongly associated with the development of PVT (19,21).

In our humble opinion, in patients without contraindications, TIPS may be preferred when thrombosis is complete, extended, chronic, when patients have a high risk of bleeding complications, or when patients are candidates for liver transplantation. It should be pointed out that the aim of the TIPS is not to normalize portal hypertension but to normalize portal

blood flow velocity. This requires only small shunts (6–8 mm) with a very little reduction in the pressure gradient. Finally, the Lv *et al.* study as well as other studies in patients with liver cirrhosis and PVT remain underpowered to demonstrate a clear role, benefits such as impact on survival, and risks of TIPS over EBL + drug therapy. There is undoubtedly a need for a larger prospective cohort studies to assess the impact of PVT in cirrhotic patients and the selection of the best treatment modality and its subsequent effect on liver transplantation outcome.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/amj.2018.01.10
Cite this article as: Ahmed R, AbuLeil B, Rayyan Y. Advances in the treatment of esophageal varices: assessing covered tips versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in patients with portal vein thrombosis. AME Med J 2018;3:32.

