

# Transjugular portosystemic stent shunt in treatment of liver diseases

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## INTRODUCTION

More than 10 years ago, an interventional technique for the creation of an intrahepatic decompressive shunt between a branch of the portal vein and a main hepatic vein using expandable metallic stents has been introduced for the treatment of portal hypertension<sup>[1,2]</sup>. This transjugular portosystemic intrahepatic stent shunt (TIPS) functions as a side to side shunt, similarly to surgical shunts. During the last decade, TIPS has become one of the major therapeutic options for patients suffering from the most common complications of liver cirrhosis, namely recurrent intestinal bleeding and refractory ascites. At present it is probably the most frequently performed portosystemic shunt procedure. TIPS insertion does not require abdominal surgery and has a lower procedure related mortality than conventional surgical shunts. In specialized centers, the rate of procedure related deaths is not higher than 1% as compared to 3%-15% reported for surgical shunts<sup>[3,4]</sup>. Thus, critically diseased or elderly patients who are not candidates for surgical shunts may be considered for TIPS insertion. However, every portosystemic shunt procedure has the potential disadvantage that the portal liver perfusion is reduced or completely stopped which may deteriorate liver function. Therefore, TIPS has to be compared with both surgical shunts and the non-shunt treatment alternatives, namely endoscopic treatment for bleeding varices and paracentesis for the treatment of refractory ascites.

In addition to the technical expertise required to perform intrahepatic stent placement, the proper selection of patients and indications remains a crucial issue. Numerous controlled clinical trials published within the last years help us weigh the

role of TIPS among the different treatment options and to select the patients, who are most likely to benefit from this procedure.

## INTESTINAL BLEEDING

Bleeding from esophageal or gastric varices in patients with portal hypertension is still associated with a high mortality of about 30%-50%<sup>[5]</sup>. Prior to the first bleeding episode, medical treatment with unselective betablockers is the therapeutic standard in patients with a high bleeding risk, shunt procedures are not indicated for the primary prevention of bleeding<sup>[5]</sup>. Once a patient has survived the first episode of intestinal bleeding, the rebleeding rate without treatment is about 50%-70% within two years<sup>[6]</sup>. Thus, the application of therapeutic strategies for the prevention of rebleeding is mandatory. TIPS versus endoscopic treatment for the prevention of rebleeding from varices

The first line treatment for bleeding varices at most centers is endoscopic injection sclerotherapy or banding ligation. These procedures have proved effective in both treating the acute bleeding episode and preventing rebleeding<sup>[5]</sup>. Within the past years, numerous studies demonstrated that banding ligation is superior to sclerotherapy with respect to local side effects (treatment induced ulcers and bleeding), efficacy of variceal eradication, and rebleeding rate. Thus, endoscopic variceal ligation is considered to be the best established endoscopic treatment for patients with bleeding varices<sup>[7]</sup>.

However, endoscopic procedures do not reduce portal pressure and thus, even after effective variceal eradication, recurrent varices may occur or patients may develop bleeding from extraesophageal varices. Since TIPS does reduce the portal pressure by about 50%, it was assumed to be more effective for the prevention of rebleeding. To date, eight controlled trials comparing TIPS with endoscopic therapy and two meta-analyses have been published<sup>[8-17]</sup>.

Overall, according to the pooled data in the most recent meta-analysis<sup>[15]</sup>, the results of the other meta-analysis published earlier are not substantially different<sup>[17]</sup>. TIPS is superior to endoscopic treatment with respect to rebleeding. The overall rebleeding rate within 13 and 33 months

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was 21% in the TIPS-group as compared with 52% for endoscopic treatment. The number of patients needed to be treated by TIPS instead of endoscopic treatment to prevent one rebleeding episode was 3.3 (95% CI 2.6, 4.4). It was argued that the rebleeding rate in the endoscopically treated patients was rather high in these trials, probably because the centers that performed these trials are specialized in TIPS rather than in endoscopic treatment. Indeed, in trials comparing different endoscopic techniques for the prevention of rebleeding, the rebleeding rates for both sclerotherapy and banding ligation were lower (approximately 40%)<sup>[7]</sup>. However, since the pooled rebleeding rate for TIPS was only 21% in the published trials, and it may even be better today because of improved patients' surveillance, it can be concluded that TIPS is more effective than endoscopic treatment for the prevention of rebleeding. On the other hand, TIPS significantly increased the encephalopathy rate (31% versus 19% after endoscopic treatment). When 4-10 (95% CI) patients are treated by TIPS instead of endoscopic treatment, one more encephalopathy rate occurs. Only one trial that had been included in the meta-analysis in abstract form but has recently been published in full text demonstrated a significant reduction of mortality after TIPS<sup>[16]</sup>. In the meta-analysis, mortality was not significantly different between the TIPS and endoscopic groups. The most common cause of death among those patients treated with TIPS was liver failure, whereas variceal rebleeding was the most common cause of death in endoscopically treated patients<sup>[15]</sup>. Thus, with respect to bleeding related mortality, there was a trend in favor of TIPS, which, however, was not statistically significant<sup>[15]</sup>.

In conclusion, TIPS is more effective for the prevention of rebleeding as compared to endoscopic treatment. This does, however, not translate into a reduction of mortality, most likely because TIPS may deteriorate liver function in some patients as indicated by a higher encephalopathy rate. Most centers prefer endoscopic banding ligation as first line treatment of bleeding esophageal varices and insert a TIPS when the endoscopic treatment fails (rebleeding despite endoscopic treatment). The clinical decision to change the therapeutic strategy from endoscopy to TIPS requires an exact evaluation of the patient's bleeding history and liver function. The severity of bleeding episodes, the prior endoscopic treatment and the site of bleeding have to be taken into account, e.g., one might change earlier from endoscopic treatment to TIPS in patients bleeding from gastric varices since they are more difficult to treat endoscopically and often bleed more severely than esophageal varices.

Furthermore, TIPS is also effective in patients with ascites. In patients with recurrent variceal bleeding and concomitant severe ascites, it is reasonable to insert a TIPS earlier since these patients may also benefit with respect to ascites.

However, patients with a decompensated liver disease (bilirubin >85.5  $\mu\text{mol/L}$ , Child's class C, a history of hepatic encephalopathy unrelated to bleeding) are likely to further deteriorate after TIPS insertion as compared to patients with a preserved liver function. These patients are not candidates for elective TIPS-insertion.

### ***TIPS versus propranolol for the prevention of rebleeding***

Propranolol effectively reduces portal pressure and related risk of rebleeding. Studies comparing unselective beta-blockers with TIPS for the prevention of rebleeding are lacking. Thirty to 40 percent of patients do not respond to propranolol with an adequate decrease of portal pressure. In a meta-analysis of nine randomized trials endoscopic sclerotherapy (which is inferior to ligation) has been shown to be more effective than propranolol to prevent variceal rebleeding<sup>[18]</sup> and TIPS is more effective than endoscopic treatment for this indication<sup>[15]</sup>. Thus, although there are no controlled trials on this topic, one may indirectly conclude that TIPS must be more effective for the prevention of variceal rebleeding than unselective beta-blockers.

### ***Emergency TIPS for the treatment of uncontrolled bleeding***

Uncontrolled acute variceal bleeding despite adequate first-line endoscopic treatment with or without vasoactive drugs continues to be a major clinical problem. The prognosis of these patients is poor and only the early diagnosis and treatment of an uncontrolled bleeding or an early rebleeding may improve the outcome.

Once the diagnosis of an uncontrolled bleeding despite adequate first-line treatment is made (which should be based on the Baveno criteria<sup>[19]</sup>, emergency TIPS is recommended as second line treatment<sup>[20]</sup> since it is effective in both reducing portal pressure and arresting bleeding in >90% of patients<sup>[21]</sup>. However, since these critically ill patients frequently develop severe complications (e.g., sepsis, pneumonia, respiratory failure, hepatorenal syndrome) although the bleeding is controlled after TIPS, only about 50% of patients survive for more than two months after emergency TIPS insertion according to most series<sup>[21]</sup>.

### ***TIPS for bleeding extraesophageal collaterals***

Some patients with portal hypertension bleed from

ectopic collaterals like duodenal or rectal varices<sup>[22]</sup>. These patients can also be effectively treated by TIPS insertion. However, atypically located varices occur more often in patients with portal hypertension due to a prehepatic obstruction like portal vein thrombosis. These patients are not candidates for TIPS, especially in patients with ectopic varices, the patency of the portal vein has to be proved prior to TIPS insertion.

#### ***TIPS for bleeding from hypertensive gastropathy***

Since hypertensive gastropathy is associated with an elevated portal pressure and chronic or *rarely*-acute bleeding from the gastric mucosa in these patients is difficult to treat with drugs or endoscopic procedures, TIPS has been evaluated for this indication. The largest recently published study found a beneficial effect of TIPS insertion with respect to rebleeding and endoscopic findings both in mild and severe hypertensive gastropathy and concerning transfusion requirements in patients chronically bleeding from severe hypertensive gastropathy<sup>[23]</sup>. This study emphasizes the importance to differentiate between patients with a real severe hypertensive gastropathy and patients with a gastric (antral) vascular ectasia (G(A)VE syndrome) because the former responds to TIPS insertion whereas the latter does not. Prior to TIPS-insertion, G(A)VE should be ruled out in these patients by endoscopy or-if necessary-by biopsy.

#### **REFRACTORY ASCITES**

The elevated portal pressure plays an important role in the pathogenesis of refractory or recurrent ascites. This clinical situation indicates a severe impairment of liver function. Thus, these patients should be evaluated for liver transplantation. If liver transplantation is not available or applicable, repeated large-volume paracentesis, implantation of a peritoneovenous shunt or TIPS insertion are the remaining treatment options.

Peritoneovenous shunting is no longer routinely performed in most specialized centers since the occlusion and infection rate is high and some studies demonstrated an even increased death rate as compared to paracentesis<sup>[24]</sup>. Repeated paracentesis is effective and safe<sup>[24,25]</sup> but is associated with some disadvantages, e.g., the risk of bacterial peritonitis or local bleeding due to frequent punctures, adverse effects of high-dose diuretic treatment, intermittent tense ascites and risk of hepatorenal syndrome.

The majority of preliminary, uncontrolled studies that applied TIPS for the treatment of refractory ascites are promising<sup>[26-30]</sup>. A recently published, larger-scale controlled randomized trial

comparing TIPS with repeated paracentesis for the treatment of refractory ascites demonstrated that TIPS is very effective for this indication<sup>[31]</sup>. Following TIPS insertion, 61% of patients had no ascites after three months as compared with 18% in the paracentesis group. In this study treatment with TIPS was independently associated with a better transplant-free survival in the multivariate analysis (one/two year transplant-free survival: 69%/58% in the TIPS group versus 52%/32% in the paracentesis group). In contrast, the only controlled randomized small study investigating the role of TIPS for the treatment of refractory ascites reported a significantly worse survival in the Child's class C patients treated with TIPS as compared to those treated with paracentesis<sup>[32]</sup>. However, since the mean baseline serum bilirubin was 30.8  $\mu\text{mol/L}$  in the patients included in the first study<sup>[31]</sup>, this discrepancy might be due to the fact that the patients in the latter study<sup>[32]</sup> had a more severe hepatic impairment. It must be stressed, that the number of patients included was relatively small in both studies<sup>[25,32]</sup> and 60<sup>[31]</sup> patients, respectively. Thus, larger studies with a higher statistical power are needed, in particular to determine the role of TIPS with respect to survival in those patients. However, it can be concluded from these two trials that TIPS is effective for the treatment of refractory ascites in patients with moderately impaired liver function (Child's class B or "good" C, serum bilirubin <51.3  $\mu\text{mol/L}$ ). In patients with a more severe liver impairment TIPS may even accelerate the progression of liver failure and worsen the prognosis.

#### ***Hepatorenal syndrome***

Patients with refractory ascites are at risk to develop a hepatorenal syndrome. This syndrome is characterized by renal insufficiency in patients with decompensated liver cirrhosis without preexistent kidney disease<sup>[33]</sup>. Especially the rapidly progressive form, in the literature commonly referred to as hepatorenal syndrome type I, has a very poor prognosis: 90% of patients died within a few weeks after diagnosis, the median survival was only two weeks<sup>[34]</sup>. Liver transplantation is the only definitive treatment for patients with hepatorenal syndrome, but many patients are not eligible for transplantation. Furthermore, due to the rapid course of this disease, even candidates for transplantation may die while waiting for a donor organ. A recent uncontrolled study evaluated TIPS in 41 non-transplant cirrhotic patients with hepatorenal syndrome (21 type I, 20 type II)<sup>[35]</sup>. The results were very promising. Even in the group of patients with type I hepatorenal syndrome, 50% of patients treated with TIPS were still alive

after six months as compared with 14% in the non-TIPS control group. TIPS cannot be recommended as an established treatment for hepatorenal syndrome before controlled randomized trials are published, but preliminary results indicate that TIPS is probably effective as a bridge to transplant for this serious condition.

### SELECTION OF PATIENTS FOR TIPS

As it has been outlined, TIPS is an effective treatment for some severe complications of liver cirrhosis. However, like every portosystemic shunt procedure, TIPS may deteriorate liver function by reducing portal liver perfusion. Thus, most studies failed to demonstrate a survival benefit in patients treated with TIPS. Especially in patients with refractory ascites, a symptom of an at least moderate to severe hepatic impairment, selection criteria have to be evaluated very carefully. For clinical practice, the serum bilirubin has proved to be an important tool for this decision. In patients with a bilirubin  $>51.3 \mu\text{mol/L}$  TIPS should be inserted only in life threatening conditions like uncontrolled variceal bleeding. In the elective situation, patients with such a severe hepatic impairment may rather benefit from non-shunt treatment alternatives. In patients with a cholestatic liver disease, higher baseline bilirubin levels may be tolerable prior to TIPS insertion. Recently, two different scoring systems for the prediction of survival after TIPS based on pre-TIPS parameters have been published<sup>[36,37]</sup>. Both scoring systems contain the serum bilirubin. In addition to serum bilirubin levels, these studies identified the following risk indicators for poor prognosis after TIPS insertion. Pre-TIPS hepatic encephalopathy unrelated to bleeding, TIPS as emergency treatment for uncontrolled hemorrhage, alanin aminotransferase levels of  $>100 \text{U/L}$ <sup>[36]</sup>, impaired renal function, prolonged prothrombine time and viral or other non-alcoholic, non-cholestatic etiology of liver cirrhosis<sup>[37]</sup>.

### SUMMARY

During the last years, TIPS has definitely gained an important role within the different therapeutic options for patients with complicated liver cirrhosis. TIPS can be recommended as second-line treatment for gastroesophageal varices that bleed despite adequate endoscopic treatment and is also beneficial in many patients with refractory ascites. TIPS insertion is recommended as emergency treatment of otherwise uncontrolled variceal bleeding. Furthermore, although controlled trials are lacking, TIPS is probably also effective in more rare conditions like hepatorenal syndrome, hepatic hydrothorax and Budd-Chiari syndrome. However,

TIPS insertion may also deteriorate liver function by reducing the portal perfusion and thus, patients have to be selected carefully.

As compared to surgical shunts, TIPS has the clear advantages of being less invasive and probably having a lower procedure related mortality. However, as indicated by the only randomized controlled trial directly comparing TIPS with a surgical shunt<sup>[38]</sup> (portocaval H-graft shunt), the relatively high TIPS-dysfunction rate due to thrombosis or endothelial hyperplasia remains a clinical problem requiring a careful follow-up of patients and should be addressed in the future development of this technique.

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