Theses of Ph.D. dissertation

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN THE TREATMENT OF PORTAL HYPERTENSION.

Dr. Lázár István

Szent-Györgyi Albert Orvostudományi Egyetem

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Introduction

The mortality of chronic liver diseases increased to more than twice in Hungary in the last couple of years. More than 8000 peoples die in every year due to the symptoms of portal hipertension[1] like variceal bleeding, hepatorenal syndrome or spontaneous bacterial peritonitis. Less life threatening but also severe sequels are refractory ascites and/or hydrothorax, hepatic encephalopathy and hepatopulmonary syndrome[2]. The decrease of the hepatocytes and the vascular failure of the liver induce a chain of deterioration regardless of the cause of the cirrhosis. The symptoms of the patients are independently divided between the vascular and parenchymal impairment of the liver. Insufficient hepatic function is exclusively treatable with liver transplantation meanwhile in the treatment of portal hypertension we have multiple alternatives,[3] like selective beta-blockers surgical portocaval shunt procedures and transjugular intrahepatic portosystemic shunt (TIPS).

TIPS was introduced in the nineties and up to now more than 130000 TIPS were performed all over the world[4]. This procedure extremely efficiently decreases portal pressure and bleeding varices can also be treated at the same time.

Procedural morbidity is lower compared to surgical shunts. TIPS is more efficient to prevent variceal bleeding compared to endoscopic methods[5] and to treat refractory ascites compared to diuretics combined with paracentesis[6,7]. TIPS presents a significant procedural challenge and needs technical skills and experiences, as well as good collaboration with internists and anesthesists and a well equipped angio suit. Since 1999 TIPS is successfully performed in Miskolc and the results are extensively published and presented both in abroad and Hungary[S3,4,7,9,12].

Purposes

1. To figure out the place of TIPS in the treatment of patients with portal hypertension and to show its advantages compared to endoscopic and surgical methods.
2. To present the technical and clinical results of TIPS in large and consecutive patient cohort.
3. To describe the rare procedural complication like the dissection of the portal vein firstly published by us and other technical difficulties and complications of TIPS.
4. To present the results with rare indications like TIPS in children, TIPS in Budd-Chiari sy. or the treatment of occlusion of the portal vein. All these were firstly performed in Hungary.
5. To describe our technical inventions performed during TIPS revisions.

6. To remind on the radiation exposure of the patients and the staff during TIPS.
7. To present our unique Hungarian 4-year-experiences with stent-grafts for TIPS.

Patients and methods

The first TIPS was performed in September 1999 at the Borsod County Teaching Hospital in Miskolc. Indications for TIPS were raised by gastroenterologists and transplant surgeons. 60% of our patients were admitted from outside of the recruitment area of the hospital. TIPS was performed in 114 patients. The gender of patients was: 66 male, 48 female (58 and 42 %). Age distribution of the patients: between 10-34 years - 7 patients, 36-44 years - 17 patients, 45-54 years - 44 patients, 55-64 years - 34 patients, >65 years – 12 patients.
Distribution of the patients according to the **Child-Pugh score**:

A: 24 patients (21%) B: 62 patients (54,4%) C: 28 patients (24,6%).

Child-Pugh classification is based on 5 parameters (serum total bilirubin, total protein, INR, the severity of ascites and hepatic encephalopathy) each of them rated 1-3 points. Scores are divided like Child-A 5-6 points Child-B 7-9 points and Child-C >10 points.
149 TIPS procedure (including revisions) were performed.

Indications of TIPS procedures:

Refractory ascites /hydrothorax		58 patients	36 %
Recurrent variceal bleeding		47 patients	29,2 %
Acute variceal bleeding		9 patients	5,6 %
Thrombosis of the portal vein		4 patients	2,5 %
Budd-Chiari syndrome		1 patients	0,6 %
TIPS revisions	42 procedures in	31 patients	26,1 %

Primary TIPS were performed according to the description of American and German interventionists[15,31]. Invasive pressure measurements were done in 72 patients TIPS (63,2 %). Systemic venous pressure was measured in the right atrium. Portal pressures (all in Hgmm) were determined in the splenic vein and the portosystemic pressure gradients were calculated. In more then 90% of the cases TIPS-200 (Rösch-Uchida) set produced by Cook, in less than 10% other sets (TJL-100 - Colapinto) were used. 25 patients underwent TIPS with Viatorr stent-grafts. Wallstents were deployed in 97 patients. Nitinol or other peripheral stents were implanted in 8 cases.

Patients were followed up every 3 months in the first year after TIPS, than every 6 months. They underwent clinical tests and Doppler ultrasonography.
Total time of fluoroscopy was documented in 69 TIPS, meanwhile DAP (dose area product) datas were worked up in 48 procedures.

Results and practical use of the results

1. <u>TIPS compared to endoscopic and surgical methods in the treatment of portal hypertension</u>
    - Despite their proven results in abroad, TIPS was not recognized in Hungary until the end of nineties. Firstly, Péter M. presented cases with short description of the method[32] but wide recognition of the technique had to wait for our published results and the proof of clinical success in large patient cohort[S3]. Due to our results TIPS became the second line therapy of patients with portal hypertension in northern Hungary.
    - The majority of Hungarian patients undergo TIPS in our cath-lab. I assisted or trained interventionists to perform the procedure in other three centers.
    - TIPS served as a bridge to successful liver transplantation in 5 of our patients. In other 4 patients TIPS made such an important clinical improvement that these patients did not need transplantation, and could be cancelled from waiting list.
    - TIPS became the treatment of choice in patients with acute subcardial variceal bleeding or those who had recurrent variceal bleeding after more then 3 sclerotherapy. All the acutely treated patients improved clinically. This needs to be emphasized, as we lost 5 patients in the waiting list for TIPS!
    - TIPS also became the method of choice in the treatment of patients with refractory ascites for 4-9 months despite maximal diuretic therapy. Our results are so convincing that 50,9% of TIPS patients were admitted with this indication.
2. <u>The success rates of TIPS</u>
    - Intrahepatic punction was successful in 97,4%. TIPS could be performed in 95,7. (The difference is coming from the cases when extrahepatic portal vein occlusion was recognized only after the punction of the portal vein). These are the best Hungarian results and also fulfill north-American requirements.
    - We achieved the demanded portosystemic pressure gradient in 94,7% of patients. The mean gradient decreased from 19,6 to 8,9 mmHg.
    - Clinical success was achieved in 88,6% of patients.

- We added 4 new indications for TIPS in Hungary: Budd-Chiari syndrome, TIPS in a child, subacute portal vein thrombosis, TIPS in transplanted liver.

3. Complications of TIPS

- Our rate of serious complications is within the ranges of recommendation according to the Society of Cardiovascular and Interventional Radiology of North America[33] (1. table):

Early complications	SCVIR recommended (%)	Own results (%)
Intraperitoneal bleeding	7	4,4
Gallbladder punction	2	1,7
Stent malposition	2	1,7
Haemobilia	2	0,8
Radiation skin injury	0,1	0
Infection	2	2,6
Hepatic artery injury	1-5	0,8
Haemolysis	10	-
Jugular hematome	5	3,5
Contrast nephropathy	5	2,6
Worsened encephalopathy	20-30	17
Pulmonary edema	1	0
Procedural mortality	<1	1,7
Late complications		
Persisting ascites	10-30	10,5
Recurrent variceal bleeding	15-25	7
TIPS stenosis (with bare stents)	50 (in the first year)	23,7

1. table: TIPS complications as recommended and our results

- We firstly ever published a procedural complication in the literature. We observed the dissection of the portal vein in 1% in our practice and published three cases[S7].

4. TIPS procedures firstly ever performed in Hungary

- The first child who underwent TIPS was a 10 years old boy with liver and renal failure of unknown etiology. He presented gastro-esophageal variceal bleedings and waited for transplantation. I performed TIPS for him in acute settings. At that time living

donor transplantation was not yet performed in Hungary, but TIPS successfully served as a bridge for transplantation Beside the size of kid (he weighted 28 kg) technical difficulties came from the preazotemic state of the patient. We injected only 30 ml of iodinated contrast medium during the procedure. No more bleeding occurred until the transplantation of both the liver and the kidneys 5 months later.

- I performed TIPS for the first time in Hungary in patient with Budd-Chiari syndrome. The patient presented with severe vascular failure of the liver and waited for transplantation. As there was no patent hepatic vein I started the punction from the intrahepatic portion of the inferior vena cava. The one year ultrasonographic control of the patient showed normal flow through the shunt. He has no symptoms at all and is not a transplant candidate anymore.
- The third newly performed procedure was a TIPS in a 41-year-old male with thrombosis of the portal vein due to protein C deficiency. He presented with refractory ascites. During the procedure we also had to perform the angioplasty of the recanalized spleno-mesenteric venous confluent in order to normalize the portosystemic pressure gradient. TIPS was technically successful but unfortunately the patient died 6 weeks later due to progressive parenchymal liver failure.

5. <u>My technical inventions performed during TIPS revisions</u>

- To decrease the symptoms of worsened hepatic encephalopathy due to TIPS I used a non-published method of narrowing the shunt. In two cases a self-expandable stent was deployed through the non-covered portion of the previously implanted stent-graft. Distal portion of this narrowing stent was placed outside of the previous. The proximal part of the stent remained inside and finally showed an hour-glass shape. So, the stent was perpendicularly deployed and decreased the inflow of the TIPS and consequently increased the portosystemic pressure gradient.
- The other invention helped to recanalize an occluded shunt. For anatomic reasons there was no chance to get into the lumen of the TIPS from the proximal part. Finally I made a punction with a liver biopsy needle through the sidewall of the TIPS and got into the portal vein. The new TIPS performed through the mashes of the previous stent kept normal flow for two years. The patient is free of symptoms and is not a candidate for liver transplantation anymore.

6. The radiation exposure of the patients and the staff during TIPS

- The mean DAP was 6181 (546-17999) Gy/cm2, the mean skin dose was found to be 583 (66-2151) mGy. Total fluoroscopy mean time was 24,5 minutes (6,8-83 min.). According to these datas TIPS is one of the procedures with the highest radiation exposure for the patients. However, we did not experience skin erythema or other skin reaction.
- We regularly use all of the available radiation protection devices and none of the film dosimetric studies of the staff showed significant elevation of irradiation. My own body exposure datas from the last years are:
  2002: 0,23 mSv 2003: 0,14 mSv 2004: 0,18 mSv 2005: 0,25 mSv,
  2006: under noticeable (These datas were accumulated during all of angiographic workload – more than 1000/year - not only TIPS.)

7. Experiences with stent-grafts for TIPS

- We used stent-grafts for TIPS in a uniquely large number of cases in Hungary, which is also in international comparison a significant number. The reason was to improve long-term results and to prevent or treat procedural complications. Since July 2002 TIPS was performed in 80 patients. 25 of them (31,25%) underwent TIPS or revision with PTFE-covered stent-graft.

Our indications for the use of stent-graft were:

1. Longer life expectancy according to liver function (Child-Pugh A,B)
2. Younger age - 44,7 years (33-59) – mean age of our other patients 52,7 years
3. Complicated procedure makes early shunt failure likely (i.e. biliary punction)
4. Budd-Chiary sy.
5. Recurrent revisions

- Only two of the 25 implanted grafts failed. One patient developed portal thrombosis 5 months later so the lack of inflow was the cause of TIPS failure. The other patient developed hepatocellular carcinoma and subsequent portal vein thrombosis 4 months after TIPS. For this reason we did not try to recanalize the shunt.
- The rate of encephalopathy which necessitated narrowing of the shunt was not higher (8%) than in TIPS cases with bare stents.
- Revisions were indicated far less frequently than in TIPS with bare stents. They were necessary only in false positive follow up diagnostic results. (One early control when

ultrasound could not penetrate the grafts due to captured air bubbles. The other was due to a misinterpreted CT in an inexperienced institution.)

- Two stent-graft patients were transplanted since. Both of them developed progressive liver failure (primary biliary cirrhosis and persisting B-virus hepatitis). The transplantation was not complicated by the TIPS stent-graft in any of them[34]. Consequently, it seems to be clear that using stent-graft for proper indications can significantly decrease the expenses of health care system and increase life-chances of cirrhotic patients.

Conclusions

1. <u>The place of TIPS in the treatment of patients with portal hypertension.</u>
   - TIPS is proved to be the most effective method to decrease portal hypertension[35,36]. It is more invasive and more expensive than endoscopic methods, therefore only in case of clinical failure of the latter is indicated[37,38].
   - The advantage of TIPS is being more efficient to prevent recurrent variceal bleeding than endoscopic ligation or sclerotherapy or non-selective ß-blockers like proplanolol[37,38]. The likelihood of recurrent variceal bleeding is found to be 19% after TIPS while 47% with endoscopic treatment[5]. Recent improvements result in less than 30% recurrence rate but using stent-grafts for TIPS can improve the results even more, below 10%[22-24]. Nevertheless, TIPS with bare stent do not improve the survival of patients[39]. The preliminary results of the use of stent-grafts seem to strongly suggest that this is going to be changed.
   - In the treatment of refractory ascites TIPS has 79% efficacy after 6 months, while repeated paracentesis only 24%[40]. TIPS procedural morbidity is so much lower than the morbidity of surgical shunts (i.e. Denver) that the latter are less and less practiced.
2. <u>Technical results of TIPS</u>
   - TIPS procedure has lot of technical difficulties. For the expected results we have to (a) carefully select patients (b) carry out the procedure in a controlled and standardized way (c) to monitorize patients during TIPS and the next 6 hours.
   - The interventionist who has carried out the TIPS procedure has to follow the clinical course of the patients as well. Technical and clinical success, as well as the rate of complications have to be continuously checked. Significant prolongation of hospital

stay, the need of intensive care, definitive failure of any organ or death in 30 day has to be concerned as major complication. They altogether must not exceed 5%.

Expected rates of success[33]:

Technical success: (Patent intrahepatic shunt)	**95%**
Hemodynamical success:	
(Expected decrease of the portosystemic pressure gradient)	**95%**
Clinical success: (Significant decrease of symptoms.)	**90%**

3. Intraoperative complications of TIPS

We have to face numerous difficulties during this challenging procedure[41].

- During jugular vein punction nerve injury, pneumothorax, neck hematoma, pseuodaneurysm of the carotid arteries can occur. Most of them can be prevented with ultrasonographic guidance, placing the patient into Trendelenburg position and asking him to perform Valsalva maneuver.
- During catheterization of the hepatic vein arrhythmia (guidewire or introducer in the right atrium) can occur. Guidewire can buckle in the atrium and devices intended to push through can even perforate the heart.
- Left liver lobe or segment I. hypertrophy can raise anatomic difficulties. Hepatic veins run almost horizontal in cases of tense ascites as well. Left jugular vein approach and paracentesis can ease these situations.
- Localization of portal branch as a target of intrahepatic punction can be made by iodinated contrast material or CO_2 injection into the wedged hepatic vein catheter. During this step of the procedure subcapsular haematoma or even severe liver laceration can occur. The bleeding site has to be promptly embolized and stent-graft deployment can also decrease the bleeding.
- The most critical moment of TIPS creation is intrahepatic punction. We can observe extrahepatic punction, biliary punction, extrahepatic portal punction or hepatic artery punction. The most important is to recognize them and alert the anesthesiologist. At the same time we have different tools to deal with the complication (embolization, balloon tamponade, stent-graft deployment, blood transfusion). The most dangerous complication is the punction of an extrahepatic portal branch because the next step is the dilatation of the punctured branch. If it is not tamponnated by the liver this carries

a real risk of bleeding to death. The extrahepatic punction itself can be clinically silent if treated with stent-graft placement[42].

- We published firstly ever in the literature the rare complication of portal vein dissection during TIPS[S7]. Our explanation is that portal pressure in our patients was measured 32-44 mmHg instead of the physiologic 10-12 mmHg and this can produce significant change in the wall of large veins, like portal vein. This extreme pressure makes the thin internal elastic membrane surrounded by smooth muscular fibers less compliant because of fibrosis. According to our experiences it may develop – similarly to the arteries – a dissection along this layer during punction or more likely due to the direct perpendicular force applied on the guidewire at the end of the needle. Dissection can result in exactly the same consequences like in the arteries. We have, for instance, a well documented case of pseudoaneurysm formation.
- During stent placement migration or malposition can occur. It is very important to let the proximal part of the stent free for a subsequent catheterization because the need for TIPS revision is quite high later on. We have to keep in mind also an eventual liver transplantation. That is why the stent must not encroach on the lumen of inferior vena cava and must not reach the confluent of superior mesenteric vein and splenic vein in order not to interfere with a future clamping by transplantation. Using stent-grafts we have to make correct measurements not to obstacle the blood flow with the covered part of the graft in the main portal branch or in the inferior vena cava.
- Dilating a TIPS stent: overdilation should be avoided not to provoke hepatic encephalopathy. Wallstent has known ability to selfdilate over 24 hours. Using stent-grafts we don't have to count on late restenosis. There will not be anything to decrease the flow through an over dilated shunt.
- Variceal embolization is routinely part of TIPS in case of the treatment of acutely bleeding patients. Embolizing agents can be moved to pulmonary circulation through the varices[41]. When using acrilates, solidified glue may attach to the end of the delivery catheter and by pulling back the catheter, the glue can be detached and obstacles splenic vein or even the TIPS channel.

4. <u>TIPS procedures firstly ever performed in Hungary</u>

- TIPS can be safely performed even in high-risk situations in the hand of experienced interventionist, who treats a reasonable number of patients yearly. The angio suit has to possess all the materials potentially needed and the operator has to check up the

results time to time for quality improvements. It is clearly demonstrated with the case of a 19-year-old girl who presented with Budd-Chiary syndrome a couple of years ago. She could not be transplanted soon after and 3 months later bled to death from her subcardial varices. 3 years later – as we possessed stent-graft and had more experiences – a successful TIPS was performed in the same clinical scenario. This fortunate patient is not even a transplant candidate anymore[48].

5. My technical inventions performed during TIPS revisions

I firstly described two technical points make TIPS revisions possible or more successful in difficult situations. Both of them have proved midterm results already.

- Inner PTFE covering of stent-grafts result in an extremely smooth surface. Thus, stents used for narrowing to reverse hepatic encephalopathy can easily migrate. Stent migration towards the heart is practically impossible with my method. Beside, there is a potential disadvantage because theoretically the blood which is flowing through the mash of the stent may hemolyse. Erythrocytes already damaged by the impaired liver function can be crushed at the metal mash of the stent and finally eliminated by the spleen[49]. This type of hemolysis is not severe and self-limited in most of the cases.
- My second invention for revision of a thrombosed TIPS has obviously alternatives. The parallel TIPS between the left hepatic vein and the left portal branch is a known tool as a supplement for the previously performed TIPS if the function of the former was not sufficient to decrease the portosystemic pressure gradient[50] We also had such a case performed to replace the right sided TIPS which had been occluded several times due to unfavorable anatomy. Despite this successful case – having known the technical difficulties of that – I am convinced that it is reasonable to try firstly my new method to regain the patency of the thrombosed TIPS. Procedural risk seems to be lower and at the same time we can reserve the chance for the patient to undergo an eventual left sided TIPS if it was going to be inevitable.

6. The radiation exposure of the patients and the staff during TIPS

- There are few datas in the literature concerning radiation doses of patients and staff during TIPS. Our measures for patients proved no higher entry skin dose than 3 Gy (limit of depilation). The results of an American study covering 135 TIPS procedure found 38,7 min. average fluoroscopy time and 2039 mGy cumulative skin dose[51]. Comparing our result (24,5 min. fluoroscopy and 583 mGy) with these there is no reason to be unsatisfied.

7. Experiences with stent-grafts for TIPS

- TIPS performed with bare stents during the first 10 years after the introduction of the procedure resulted in disappointment with the long-term results[7,29,35]. Reintervention rate and additional cost with that was very high[44]. The average one-year patency without revision was found to be no more than 69%[53]. Stent-grafts raised that number up to 85-90% and the secondary one-year patency from 85% up to 98%[22-24, 54]. Only the bile impermeable ePTFE-covered grafts achieved such a favorable result. Others, like PET-covered grafts developed not specifically for TIPS did not improve the patency rate[54].
- Control ultrasonography after TIPS with stent-graft is indicated only in case of recurrent clinical signs or no more frequently than every 6 months according to my results.
- The rate of worsened hepatic encephalopathy was not higher with stent-grafts than with bare stents. It can be explained by the fact that grafts are dilated to a smaller diameter having known that they are significantly less prone to in-stent restenosis.
- Our 90% primary one-year patency rate with grafts suggests that stent-grafts significantly decrease the reintervention rate and the cost of the treatment. At the same time long term success makes gastroenterologist and transplant surgeons more confident with this method.

We can conclude, that TIPS is safe method to treat portal hypertension with lower morbidity and higher efficacy than surgical or endoscopic methods. Proper indications, experience-based patient choice, technical developments like stent-grafts improved long-term patency and widened the acceptance of TIPS. We have to prove the economical efficacy and make the method better known and available all over in Hungary. These are the key points to better treat hundreds of patients with impaired liver function and make their life expectancy longer.

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