Transjugular intrahepatic portosystemic shunt in liver transplant recipients

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Abstract

AIM: To evaluate the efficacy of transjugular intrahepatic portosystemic shunts (TIPSs) after liver transplantation (LT).

METHODS: Between November 1996 and December 2005, 10 patients with severe recurrent hepatitis C virus infection ($n = 4$), ductopenic rejection ($n = 5$) or portal vein thrombosis ($n = 1$) were included in this analysis. Eleven TIPSs (one patient underwent two TIPS procedures) were placed for management of therapy-refractory ascites ($n = 7$), hydrothorax ($n = 2$) or bleeding from colonic varices ($n = 1$). The median time interval between LT and TIPS placement was 15 (4-158) mo.

RESULTS: TIPS placement was successful in all patients. The mean portosystemic pressure gradient was reduced from 12.5 to 8.7 mmHg. Complete and partial remission could be achieved in 43% and 29% of patients with ascites. Both patients with hydrothorax did not respond to TIPS. No recurrent bleeding was seen in the patient with colonic varices. Nine of 10 patients died during the study period. Only one of two patients, who underwent retransplantation after the TIPS procedure, survived. The median survival period after TIPS placement was 3.3 (range 0.4-20) mo. The majority of patients died from sepsis with multiorgan failure.

CONCLUSION: Indications for TIPS and technical performance in LT patients correspond to those in non-transplanted patients. At least partial control of therapy-refractory ascites and variceal bleeding could be achieved in most patients. Nevertheless, survival rates were disappointing, most probably because of the advanced stages of liver disease at the time of TIPS placement and the high risk of sepsis as a consequence of immunosuppression.

INTRODUCTION

Since the first attempts were made over 30 years ago, placement of transjugular intrahepatic portosystemic shunts (TIPSs) has become an established procedure in patients with complications of portal hypertension[1]. The two main indications for TIPS are therapy-refractory ascites and variceal bleeding unresponsive to endoscopic treatment[2-7]. In many patients with these complications,

TIPS is used as a bridge to liver transplantation (LT). In contrast, there is rather limited experience with the use of TIPS following LT. One reason is the rare occurrence of portal hypertension after LT. The causes of portal hypertension in such patients can be impaired venous outflow, recurrence of the underlying liver disease, size mismatch between donor and recipient organs and/or vessels[8,9], or increased vascular resistance as a consequence of repeated rejection episodes[10]. This might result in the development of ascites, hepatic hydrothorax or variceal bleeding comparable to the non-grafted population. Therapeutic options for these conditions are basically the same, including TIPS. The placement of a TIPS can be rendered more difficult by the altered anatomy after transplantation. Furthermore, patients undergoing chronic immunosuppression are at higher risk of infection.

Only few data have been published on TIPS after LT and its role in LT recipients is largely undefined. The aim of our retrospective analysis was to critically scrutinize the indications, efficacy and safety of TIPS placement in liver recipients at our center.

MATERIALS AND METHODS

Between November 1996 and December 2005, a total of 11 TIPSs were placed in 10 liver recipients at Innsbruck Medical University Hospital, which represents 5% of all 217 TIPS procedures carried out during this time period. One of the patients received a TIPS before and after retransplantation. The mean age of the six male and four female patients was 56.8 (37-71) years. The underlying liver diseases were hepatitis C virus (HCV) cirrhosis ($n = 4$), alcoholic liver disease ($n = 2$), primary biliary cirrhosis ($n = 2$), hemochromatosis ($n = 1$) and autoimmune hepatitis ($n = 1$).

Patients underwent full-sized deceased donor LT, three of them using a piggyback technique, and the remaining patients by replacement of the retrohepatic vena cava. The mean time interval between LT and TIPS was 29.7 mo (range: 3.8-158 mo). In four patients, recurrent HCV cirrhosis was present at the time of TIPS implantation, five had ductopenic rejection, and one had portal vein thrombosis.

Therapy-refractory ascites was the indication for TIPS in seven patients, resistant hydrothorax in two, and bleeding from colonic varices in one. Ascites and hydrothorax were assessed by ultrasound and chest X-ray, respectively.

All four patients with recurrent HCV presented with decompensated cirrhosis at the time of TIPS implantation. One patient was in Child-Turcotte-Pugh class B and three were in class C. The median model for end-stage liver disease (MELD) score for all patients was 20 (12-35).

The TIPS procedure used for LT recipients did not differ from that for non-transplanted patients, as described previously[6,7].

The immunosuppressive regimen at the time of the TIPS procedure consisted of calcineurin inhibitors,

alone ($n = 1$) or in combination with steroids ($n = 2$), mycophenolate mofetil (MMF; $n = 3$), or an mTOR-inhibitor ($n = 1$). An mTOR-inhibitor was used with MMF in one patient or with low-dose steroids in three patients.

Variables were compared using Student's t test, and $P < 0.05$ was considered statistically significant. Kaplan-Meier plots were calculated using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

TIPS were placed in all patients without any procedural complications. One patient with pre-existing atrial fibrillation developed cardiac failure during the procedure but responded to specific treatment.

The mean portosystemic pressure gradient was reduced from 12.5 (8-22) mmHg to 8.7 (5-14) mmHg after the procedure. Although pressure gradients below 12 mmHg were found in three patients with refractory ascites and one with hydrothorax, the TIPS procedure was continued, with the aim of further decreasing the final pressure gradients (around 5 mmHg), in order to improve the clinical condition.

Regarding patients with refractory ascites, complete resolution of ascites was achieved in three and a partial response in two patients, whereas no response was seen in two others. TIPS failed to improve the condition in both patients with hydrothorax. After TIPS implantation, no more bleeding was seen in the patient who suffered from colonic variceal hemorrhage.

Seven out of 10 patients developed TIPS-related hepatic encephalopathy, which necessitated TIPS reduction in two patients with a later closure in another. In the other patients, encepaholpathy was successfully treated with standard medical therapy. One patient developed TIPS dysfunction, which was corrected by dilatation.

Only one patient in our cohort, who underwent retransplantation, survived long-term. All other patients died, mainly from sepsis associated with multiorgan failure. The median survival time of all patients was 3.3 mo (range 0.4-20 mo; Figure 1).

The course of all 10 patients is summarized in Table 1. Although TIPS was able to reduce ascites in patients 1 and 2, both died at 1 and 3 mo after TIPS placement because of HCV recurrence, with sepsis and multiorgan failure. Both patients presented with a high MELD score of 22 and 26, respectively.

The third patient with therapy-refractory ascites first responded well to TIPS. Four months later, however, she developed massive bleeding in the upper gastrointestinal tract and lungs because of severe coagulopathy, secondary to graft failure associated with ductopenic rejection, and died.

No improvement in ascites was seen in the fourth patient. Eight months after TIPS implantation, the patient underwent retransplantation for recurrent HCV cirrhosis. A few months after retransplantation, he again developed a rapidly progressive HCV recurrence, with

Table 1 Summary of clinical data and outcomes

Patient no.	Age, sex	Cause of liver disease	Transplant pathology before TIPS	Indication for TIPS	MELD score at TIPS	CPC at TIPS	Time from transplantation to TIPS (mo)	Encepha-lopathy-post-TIPS	Follow-up after TIPS
1	71, F	Hepatitis C	HCV recurrence	Ascites	22	C	15	Yes	Died 1 mo
2	59, M	Hepatitis C	HCV recurrence	Ascites	26	C	16	Yes	Died 3 mo
3	37, F	Primary biliary cirrhosis	Vanishing bile duct syndrome	Ascites	18	B	4	Yes	Died 4 mo
4	56, M	Hepatitis C	HCV recurrence	Ascites	15	C	158	Yes	ReLT 8 mo, died after ReLT, see below
	59, M	Hepatitis C	HCV recurrence	Ascites	13	C	18	Yes	TIPS reduction day 11 and 16; died at 2 mo
5	52, M	Fatty liver cirrhosis	Vanishing bile duct syndrome	Ascites	35	C	10	No	ReLT 3 mo; alive 32 mo
6	51, F	Hepatitis C	HCV recurrence	Ascites	19	B	61	No	Died 3 mo
7	71, M	Primary biliary cirrhosis	Thrombosis of the portal vein at the anastomosis	Ascites	12		4	No	TIPS revision 3 mo; died 12 mo
8	62, M	Hemochromatosis	Vanishing bile duct syndrome	Hydrothorax	21	C	17	Yes	Died 1.5 mo
9	68, M	Fatty liver cirrhosis	Vanishing bile duct syndrome	Hydrotho-rax/Ascites	30	B	11	Yes	Died 11 d
10	38, F	Autoimmune hepatitis	Vanishing bile duct syndrome + thrombosis of the portal vein	Bleeding	[1]	B	8	Yes	TIPS reduction 2.5 mo; died 19 mo

[1]MELD score calculation not possible due to incomplete laboratory data. ReLT: Liver retransplantation.
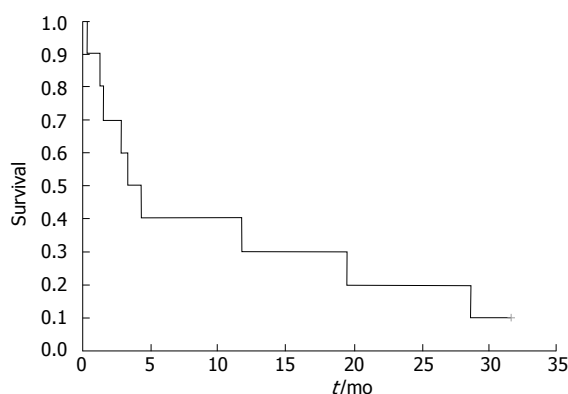

Figure 1 Kaplan-Meier plot of patients' overall survival after TIPS implantation.

massive ascites that was resistant to diuretic therapy. Therefore, 18 mo after retransplantation, a TIPS was placed again. Eleven days after placement, a reduction in the TIPS, with subsequent complete closure was necessary because of severe hepatic encephalopathy. The patient died 2 mo after the second shunt placement from sepsis with multiorgan failure.

In the fifth patient, TIPS implantation resulted in complete resolution of ascites. Three months after TIPS placement, the patient developed ductopenic rejection in association with renal failure, and underwent combined liver and kidney transplantation. Thirty-two months later, the patient is doing well with stable graft function.

The sixth patient with TIPS placement for ascites did not respond to the procedure and died 3 mo later from HCV recurrence.

Ascites further deteriorated in patient seven after TIPS placement. Shunt occlusion was suspected and the patient was given another TIPS 3 mo later, which

led to a reduction of portosystemic pressure from 19 to 12 mmHg, and disappearance of ascites. The patient, however, died 1 year after TIPS insertion from cholangitis secondary to multiple ischemic-type intrahepatic biliary strictures.

TIPS placement did not result in any improvement in the two patients with hydrothorax (patients 8 and 9). One of them died at 6 wk and the other at 11 d after TIPS, as a result of sepsis.

The patient with colonic bleeding as indication for TIPS placement developed severe encephalopathy at 2.5 mo after the procedure, which required a reduction in TIPS. The portal pressure increased from 5 to 9 mmHg, and encephalopathy improved thereafter. Although there was no recurrence of bleeding, the patient died 19 mo after TIPS because of chronic rejection.

DISCUSSION

TIPS is an established therapeutic modality for the management of complications of portal hypertension, in particular, therapy-refractory ascites or pleural effusion, as well as variceal bleeding resistant to endoscopic treatment. However, there is much less experience with TIPS after LT[11-15]. Although the indications for TIPS should be essentially the same as in patients without LT, certain specific points need to be considered.

At our center, the indications for TIPS placement did not differ between the transplant and non-transplant patients, with therapy-refractory ascites being the main indication also in LT recipients. Therapy-refractory hydrothorax and variceal bleeding, not manageable by endoscopic means, were less frequent indications. Our analysis showed that, in principle, TIPS was technically feasible in patients with portal hypertensive

complications after LT, and was efficacious in the majority of patients. Complete resolution was achieved in three out of eight patients, and a partial response in two further patients with therapy-refractory ascites. In addition, severe variceal hemorrhage in one patient did not recur after TIPS. No improvement, however, was seen in both patients with severe hepatic hydrothorax. Similar response rates have been reported in four previously published series, including a small study of 6-12 patients[11-14]. In these studies, improvement or complete resolution of ascites was achieved in 50%-90% of patients, and only two out of 10 patients with variceal hemorrhage experience recurrent bleeding.

The success rate of TIPS placement for managing ascites and variceal bleeding in LT was comparable with that in non-transplanted patients at our department. In the present cohort, complete resolution or significant reduction in the amount of ascites was achieved in about 70% of patients, and recurrence of bleeding was prevented in about 77% of patients (data not shown).

With an average survival of 3.3 mo, the survival in our series was extremely poor. This might mainly have been the result of the advanced stage of liver disease and the already poor prognosis of our patients at the time of TIPS placement, and not by the intervention itself. TIPS should serve as a bridge to a possible liver retransplantation. As we had only little experience with TIPS in LT recipients, this intervention was indicated with great caution. As a consequence, TIPS was placed in LT patients as the last therapeutic option, after all conservative modalities had failed. Several studies have shown that survival rates of TIPS patients with advanced disease are markedly poorer than those in earlier stages of liver disease[4,16,17]. In fact, almost all of our patients presented with an advanced stage of graft dysfunction and high MELD scores (median score of 20). The MELD score was originally developed for patients undergoing TIPS[18], and then slightly modified to predict survival of patients with liver cirrhosis in general[19]. In our analysis, there was a trend towards a higher MELD score being associated with poor survival. The correlation was not statistically significant, most probably as a result of the small number of patients.

It is well known that the natural course of recurrent HCV infection is more aggressive and leads more rapidly to cirrhosis of the allograft and graft failure than HCV infections in non-transplanted patients. Subsequently, the long-term outcome of HCV-positive patients after LT is worse compared to those with other indications for transplantation[20-23]. It has been shown that the prognosis of HCV patients is poor after decompensation, with a median survival of less than 1 year[20]. All of our four patients with recurrent hepatitis C infection presented with decompensated cirrhosis (Child-Pugh stage B or C and MELD scores between 13 and 26).

Chronic rejection with progressive loss of bile ducts inevitably leads to irreversible loss of the allograft[24], with liver retransplantation rates of 50%-90%[25,26]. Prognosis is especially poor in patients with bilirubin values > 10 mg/dL[27]. In our study, all three patients with chronic

rejection presented with a bilirubin above this level.

Therefore, an advanced stage of graft dysfunction caused by recurrent HCV cirrhosis and chronic ductopenic rejection might have been responsible for the poor survival rate in our patients. In addition, the number of liver retransplantations, the only potentially curative therapy for these patients, was lower in our series compared to other studies. Only two of our patients underwent liver retransplantation, whereas the retransplantation rate was 50% in the largest series of Amesur and co-workers[13]. Three of our patients died while being on the waiting list for a second LT, which suggests that retransplantation should be considered as early as possible when graft decompensation occurs.

The most frequent cause of death ($n = 5$) in our cohort was sepsis associated with multiorgan failure. Thus, two interacting factors were responsible for the frequency of sepsis in our patients. Patients with impaired liver function or recurrent cirrhosis frequently develop bacterial infections, which lead to death in 30%-50% of cases[28,29]. The risk of infection is further increased by chronic immunosuppression. Therefore, we recommend prophylactic antimicrobial therapy following TIPS placement.

The altered anatomy of the hepatic vessels that results from LT should be kept in mind before the TIPS procedure. The two most frequently used techniques are the replacement of the retrohepatic vena cava and the piggyback-type of transplantation. Previous studies have shown that there are no difficulties in TIPS placement with either of these procedures. In contrast, in patients with cava-cava liver transplantation, probing for the hepatic and portal veins in the recipient's organ might be difficult[11-14]. No technical problems were encountered in our series, in which, three had undergone the piggyback-type of transplantation and the remaining patients had replacement of the retrohepatic vena cava. This indicates that the anatomical situation in these patients creates no problems for the TIPS procedure.

Only one patient (10%) developed dysfunction of the TIPS, which was managed successfully by TIPS dilatation. In contrast, the rate of TIPS revision in our non-transplanted patients was markedly higher at 35% ($P = 0.059$). This low rate of TIPS dysfunction in the LT group might be attributed to the fact that immunosuppressive therapy can lead to reduced intima proliferation[11], but can also be ascribed to the very short survival of these patients.

Noticeable in our LT recipients was a low pre-interventional mean portosystemic pressure gradient of 12.5 mmHg, which suggests that ascites and hydrothorax post-transplant may not be as well-correlated with portal pressure as in the pre-transplant phase. Other factors beside the portosystemic pressure gradient, such as renal function, may play a major role in the efficacy of TIPS in LT transplant recipients. Chronic renal dysfunction is a common complication in transplant recipients, especially if calcineurin inhibitors are used[30]. In our cohort, both patients with hepatic hydrothorax presented with markedly impaired renal function (glomerular filtration

rate < 20 and 45 mL/min per 1.73 m², respectively), which may explain their non response to TIPS treatment, although the postinterventional pressure gradients could be successfully lowered to 10 and 5 mmHg, respectively.

In the ascites group, only three of seven patients showed normal renal function, and in two of these, complete resolution of ascites was achieved. No statistically significant correlation was found between the reduction of the portal pressure gradient and response to TIPS.

Hepatic encephalopathy developed in 70% of our patients. A similar rate of encephalopathy was also described in a previous study, and is markedly higher than the incidence reported for non-transplant TIPS recipients[4,11]. We could not find a relation between final pressure gradients and the development of encephalopathy. Mild pre-existing hepatic encephalopathy was found in two patients, and in both, a deterioration of encephalopathy was noticed after TIPS creation. Therefore, we conclude that the main reasons for the high occurrence of hepatic encephalopathy in this cohort might be the advanced stage of disease in these patients, as well as the potentially neurotoxic effects of immunosuppressive drugs, in particular the calcineurin inhibitors.

In summary, our study showed that the TIPS procedure in LT recipients was feasible without technical difficulties. Indications for TIPS seemed not to differ from those of the non-transplanted TIPS group. The TIPS procedure was efficacious in the management of therapy-refractory ascites and severe variceal bleeding unresponsive to endoscopy, in the majority of patients. TIPS did not appear to be useful in patients with hepatic hydrothorax. However, the outcome was very disappointing. The low survival rate shows that, in LT patients with an already advanced stage of graft dysfunction, TIPS does not improve prognosis. Similar to the recent work of Kim and co-workers[15], we conclude that TIPS may not be useful in most transplant patients with an advanced graft disease. It may have its place in treating some vascular problems after LT. Otherwise retransplantation remains the only possibility to improve the survival of patients with portal hypertensive complications after LT.

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COMMENTS

Background
Transjugular intrahepatic portosystemic shunt (TIPS) is a well-established therapeutic procedure in patients suffering from complications of portal hypertension, such as ascites or variceal bleeding. In rare cases, portal hypertension develops in liver transplant (LT) recipients. The use of TIPS in this special patient cohort has been discussed in the literature, but only few cases have been reported so far.

Research frontiers
In this study, the authors report a series of TIPS placements in 10 LT recipients because of ascites, hydrothorax and variceal bleeding. In the majority of patients, at least a partial response could be achieved, however, the outcome of these patients was poor with a median survival of 3.3 mo.

Innovations and breakthroughs
Portal hypertension is a rare but severe complication after LT and leads to graft loss in the majority of patients. The pathophysiology is not well understood and the best therapeutic modality for these patients remains to be defined. TIPS placement has been discussed. This paper shows that TIPS placement is not efficacious in this cohort.

Applications
Results from this study will help to refine the post-transplant care of patients and should encourage physicians to consider retransplantation as the only effective treatment in LT patients with portal hypertensive complications.

Terminology
TIPS is an interventional technique for the creation of an intrahepatic decompressive shunt between a branch of the portal vein and the main hepatic vein, using expandable metallic stents. This leads to a decrease in portosystemic pressure gradient and has become an established therapy for patients with therapy-refractory ascites and unresponsive variceal bleeding.

Peer review
This is a well written report on a single institution's experience on the use of TIPS after LT for the treatment of portal hypertension recurrence related complications. Although the series is small, the paper gives a clear message to the readers about a selected topic in liver transplantation.

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