Utility of Transjugular Intrahepatic Portosystemic Shunts in Liver-Transplant Recipients

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BACKGROUND: Transjugular intrahepatic portosystemic shunts (TIPS) have been used to control symptomatic portal hypertension in patients awaiting liver transplant. Although their role in pretransplantation patients is well established, their role in posttransplantation patients is unclear.

STUDY DESIGN: Retrospective analyses were performed for 18 liver-transplant recipients who underwent TIPS for recurrent end-stage liver disease. Patients were evaluated in regard to gender, age, diagnoses, allograft type, indication for TIPS, portal pressures, laboratory results, Model for End-Stage Liver Disease (MELD) score, and outcomes.

RESULTS: Median days from transplant to TIPS was 939 days (range, 122 to 3,415 days). Indications included variceal bleeding (n = 2) and ascites (n = 16). Ten patients (56%) responded to TIPS; TIPS prevented bleeding in both patients with varices, and it achieved symptomatic benefit in half of all patients with ascites. TIPS reduced median portal pressures from 22 mmHg (range, 17 to 50 mmHg) to 16 mmHg (range, 11 to 22 mmHg) and median portosystemic pressure gradients from 18 mmHg (range, 8 to 30 mmHg) to 8 mmHg (range, 2 to 12 mmHg). It increased median Model for End-Stage Liver Disease scores from 16 (range, 12 to 29) to 17 (range, 10 to 34) immediately and to 22 (range, 10 to 35) at 1 month. Six patients (33%) underwent retransplantation at a median of 58 days (range, 21 to 71 days) post-TIPS. Of the remaining 12 patients, 3 (25%) were alive and well at a median of 90 days (range, 78 to 1,169 days) post-TIPS; 9 (75%) died at a median of 99 days (range, 13 to 1,400 days) post-TIPS. Subgroup analysis failed to demonstrate significant differences between patients whose ascites responded to TIPS (n = 8) and patients whose ascites did not (n = 8). Responders were younger, had higher baseline portal pressures, greater reductions in portal-systemic pressure gradients, and better hepatic function.

CONCLUSIONS: Though small, this was the largest series to date of TIPS in liver-transplant recipients. Overall, 56% of patients responded to TIPS. No single factor predicted response or nonresponse of ascites to TIPS. Without retransplantation, 75% of patients died. Careful selection is necessary when considering TIPS for patients with ascites. (J Am Coll Surg 2009;208:539–546. © 2009 by the American College of Surgeons)

Transjugular intrahepatic portosystemic shunts (TIPS), which establish artificial conduits between branches of the portal and systemic venous systems within the liver parenchyma, were first described in experimental models in 1969 and in clinical practice in 1989.[1,2] In the past 20 years, TIPS have been placed in patients with cirrhosis and end-stage liver disease (ESLD) in an effort to control the symptoms of portal hypertension. Although TIPS do not slow or stop disease progression and, indeed, may hasten hepatic failure, they often mitigate life-threatening or debilitating symptoms. The most common indications include variceal bleeding, refractory ascites, hydrothorax, and Budd-Chiari Syndrome.[3-5] One study demonstrated that in patients with refractory ascites, TIPS offered survival advantages over intermittent large-volume paracenteses.[3] In other words, although they do not control or cure hepatic failure, TIPS proved to be attractive and effective bridges to eventual hepatic transplantation.

Initially, when TIPS were placed in patients awaiting hepatic transplant, concerns were raised over the technical feasibility of transplant. It was believed that TIPS might distort the venous vasculature of the liver—its portal inflow

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Abbreviations and Acronyms

ESLD = end-stage liver disease
EtOH = ethanol
GI = gastrointestinal
HBV = hepatitis-B virus
HCV = hepatitis-C virus
INR = international normalized ratio
MELD = Model for End-Stage Liver Disease
TIPS = transjugular intrahepatic portosystemic shunts

or hepatic outflow—complicating or precluding orthotopic hepatic allograft. Subsequent data suggested otherwise: TIPS did not hinder operations and offered patients and surgeons a period of symptomatic benefit before surgery.[6,7]

As TIPS were more frequently implemented, other benefits became apparent. Because TIPS were placed percutaneously and safely, they largely supplanted other vascular shunts, which had been placed surgically. In addition, TIPS could be placed in patients in extremis, including patients with active variceal bleeding and advanced hepatic failure; the same was not true for surgical shunts. In addition, TIPS potentially relieved both bleeding and ascites, but surgically placed shunts relieved only the bleeding.

With cumulative successes in surgical techniques and immunosuppressive pharmacotherapies, the population of patients with liver transplants has been increasing.[8] Despite these gains, for these patients, ESLD may recur as a function of allograft failure or recurrent or de novo disease; rejection, small-for-size syndrome, venous obstruction (including Budd-Chiari syndrome), and recurrent or de novo viral hepatitis may give rise to posttransplant ESLD. So like their preliver-transplant counterparts, some postliver-transplant patients may develop portal hypertension and the symptoms thereof. For these patients, three options are available: nonoperative management (for ascites: diuretic pharmacotherapies, fluid and salt restriction, and paracenteses; and for variceal bleeding: endoscopic banding and sclerotherapy); retransplant; and TIPS. These treatment modalities are not mutually exclusive and may be used concomitantly or in succession. Indeed, as with the preliver-transplant population, in the postliver-transplant population, TIPS may serve as bridges to retransplant or as definitive treatments in and of themselves.

These two groups of patients—liver-transplant recipients in whom TIPS serve as bridges to retransplant and liver-transplant recipients in whom TIPS are definitive therapies—are the focus of a small number of studies with small study populations. These consist largely of case reports, case series, and retrospective reviews.[5,9-16] Nevertheless, with increasing numbers of liver-transplant recipients, more and more of this population may very well experience recurrent ESLD and symptomatic portal hypertension, and they may require TIPS.

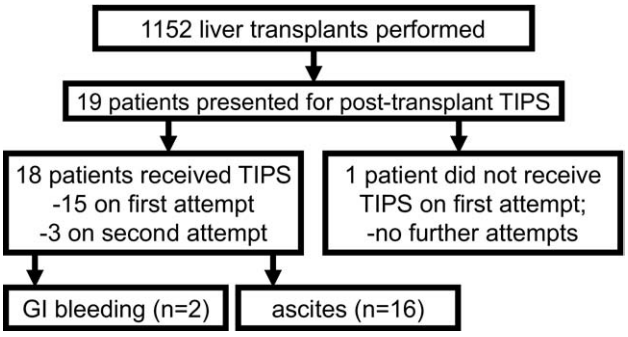

Figure 1. Diagram of study population.

The goals of this work were to add to this body of literature with the University of Rochester's experience with TIPS in liver-transplant recipients, to determine the immediate and longterm outcomes of TIPS in this population, and to determine factors associated with response or nonresponse of ascites to TIPS.

METHODS

The Department of Surgery and the Internal Review Board of the University of Rochester approved this study. Throughout, strict security of protected information was maintained.

A chart review was carried out for all patients who had undergone liver transplantation during a 10-year period (1996 to 2006; Fig. 1). From this group of 1,152 patients, a subset of 18 patients who had TIPS placed after hepatic allograft was determined. Medical records for this group were reviewed and data were collected retrospectively. Examined factors included gender, age, diagnoses and indications for liver transplant and TIPS, type of allograft, time from transplantation to TIPS, pre- and post-TIPS portal and systemic pressure measurements, serum laboratory values (for albumin, international normalized ratio [INR], creatinine, bilirubin, ammonia), Model of End-Stage Liver Disease (MELD) scores, and clinical outcomes. Lower MELD scores indicated less severe ESLD and vice versa. Patients were followed for a median of 69 days (range, 13 to 1,400 days) from TIPS to retransplantation, survival, or death.

Posttransplantation patients who underwent TIPS for refractory ascites were studied in detail (n = 16). Responders (patients whose ascites responded to TIPS, n = 8) and nonresponders (patients whose ascites did not respond to TIPS, n = 8) were compared. Statistical analyses included Fisher's exact test for discrete variables and Student's *t*-test for continuous variables. All discrete variables were summarized as counts and percentages; all continuous

Table 1. Survey of Pretransjugular Intrahepatic Portosystemic Shunt Patient Demographics

Indication for TIPS	Age, y, gender	Donor type	Pretransplant disease	Posttransplant disease	Post-TIPS outcomes
GI bleeding	63, M	Deceased	HBV	Recurrent HBV	Retransplant at 26 d
GI bleeding	16, M	Live	Cystic fibrosis	Small-for-size syndrome	Alive at 78 d
Ascites	50, M	Deceased	HCV	Recurrent HCV	Retransplant at 59 d
Ascites	48, M	Deceased	HCV	Recurrent HCV	Retransplant at 67 d
Ascites	48, M	Deceased	HCV	Recurrent HCV	Death at 208 d
Ascites	49, F	Deceased	HCV	Unknown	Death at 191 d
Ascites	52, M	Deceased	HCV	Recurrent HCV	Death at 1,400 d
Ascites	53, M	Deceased	HCV	Recurrent HCV	Alive at 90 d
Ascites	47, M	Deceased	HCV	Recurrent HCV	Retransplant at 71 d
Ascites	49, F	Deceased	HCV	Recurrent HCV	Alive at 1,169 d
Ascites	55, M	Deceased	HCV	Recurrent HCV	Death at 13 d
Ascites	63, M	Deceased	EtOH	Unknown	Death at 15 d
Ascites	42, F	Live	EtOH	Unknown	Death at 99 d
Ascites	56, M	Deceased	HCV	Recurrent HCV	Death at 946 d
Ascites	52, M	Deceased	EtOH	De novo HCV	Retransplant at 57 d
Ascites	55, M	Deceased	HCV	Recurrent HCV	Death at 23 d
Ascites	46, M	Deceased	HCV	Recurrent HCV	Retransplant at 21 d
Ascites	56, F	Deceased	Sarcoidosis	Recurrent sarcoidosis	Death at 38 d

All patients are presented; n = 18.
EtOH, ethanol; F, female; GI, gastrointestinal; HBV, hepatitis-B virus; HCV, hepatitis-C virus; M, male; TIPS, transjugular intrahepatic portosystemic shunts.

variables as medians with ranges. Differences were considered significant if p values were less than 0.05. Multivariable analyses were not possible in light of a small study population. Statistical analyses were performed using commercially available software (MedCalc for Windows [MedCalc Software]).

RESULTS

Review of hospital records and data from the United Network for Organ Sharing demonstrated that between 1996 and 2006, 1,152 liver transplantations were performed at the University of Rochester (Fig. 1). Of these patients, 19 (1.6%) presented with symptomatic portal hypertension and were deemed suitable candidates for TIPS; ultimately, 18 patients had TIPS successfully placed. Median time from transplantation to TIPS for these patients was 939 days (range, 122 to 3,415 days).

The median age was 51 years (range, 16 to 63 years; Table 1). There were 14 men (78%) and 4 women (22%). Infection with hepatitis-C virus (HCV), seen in 12 patients (67%), was the most common diagnosis. Alcoholic (EtOH) hepatitis and cirrhosis were seen in 3 patients (17%). Hepatitis-B virus (HBV) infection was seen in 1 patient (6%), cystic fibrosis in 1 patient, and sarcoidosis in 1 patient. Sixteen patients (89%) received deceased-donor allografts; 2 patients (11%) received live-donor allografts.

Of 13 patients with viral hepatitis (HBV or HCV), 12 (92%) had recurrent disease documented by serum viral titers in the setting of cirrhosis and portal hypertension (Table 1). One patient with HCV infection did not have positive viral titers and a cause for recurrent ESLD was not determined. Another patient, who had initially undergone liver transplantation for EtOH cirrhosis, had de novo HCV; he denied EtOH remission. Two other patients, who had undergone liver transplantation for EtOH cirrhosis, and who also denied remission, had no known causes for recurrent ESLD. One patient had small-for-size syndrome; one had recurrent sarcoidosis.

Indications for TIPS included gastrointestinal (GI) bleeding (n = 2) and refractory ascites (n = 17; Fig. 1; Table 1). In patients presenting with GI bleeding, endoscopy failed to demonstrate any active or imminent hemorrhage. Before endoscopy, both patients had had bleeding sufficient to decline to physiologic extremis, so TIPS were placed in an effort to prevent further, potentially life-threatening, bleeding. In patients presenting with ascites, pharmacologic and dietary management failed. These patients required repeated paracenteses. For them, TIPS were placed in an effort to eliminate the need for further large-volume paracenteses.

Of 19 patients, 18 (95%) underwent successful TIPS placement —15 on first attempt and 3 on second attempt (Fig. 1). (In one patient, the interventional radiologist was

unable to place a TIPS; no further attempts were made.) Failures occurred for one of two reasons: technical inability and patient instability. Indeed, two patients experienced bleeding sufficient to require admission to an ICU; one of these patients also required exploratory laparotomy. Of 18 patients with TIPS, 5 patients required revision; of these, 4 patients had strictures (1 with associated thrombus and 3 without), and 1 patient had subsequent encephalopathy and elevated serum ammonia levels. One patient required eight revisions, all of which were stricturoplasties.

Portosystemic venous pressure gradients

Median pre- and post-TIPS portal pressures were 22 mmHg (range, 17 to 50 mmHg) and 16 mmHg (range, 11 to 22 mmHg), respectively. Median reduction in portal pressures was 7 mmHg (range, 1 to 38 mmHg); this represented a median decrease of 28% (range, 5% to 76 %). In addition, median pre- and post-TIPS portosystemic pressure gradients were determined:18 mmHg (range, 8 to 30 mmHg) and 8 mmHg (range, 2 to 12 mmHg), respectively. The median absolute reduction was 10 mmHg (range, 5 to 18 mmHg); the median relative reduction was 60 % (range, 38% to 75%). All 18 patients had reductions of their portal pressures and portal-systemic pressure gradients.

Laboratory values

Median baseline albumin was 2.6 g/dL (range, 1.6 to 3.9 g/dL). Median baseline (24 hours pre-TIPS), immediate (24 hours post-TIPS), and longterm (1 month post-TIPS) INR, creatinine, and bilirubin were obtained and used to calculate corresponding MELD scores. Median baseline, immediate, and longterm values were, respectively: INR, 1.2 (range, 1.0 to 1.6), 1.3 (range, 1.0 to 2.0), and 1.3 (range, 1.0 to 2.0); creatinine, 2.0 mg/dL (range, 0.8 to 4.9 mg/dL), 1.8 mg/dL (range, 0.8 to 5.1 mg/dL), and 1.7 mg/dL (range, 0.7 to 8.1 mg/dL); bilirubin, 0.7 mg/dL (range, 0.2 to 26.7 mg/dL), 1.9 mg/dL (range, 0.3 to 27.6 mg/dL), and 1.8 mg/dL (range, 0.8 to 30 mg/dL); and MELD, 16 (range, 12 to 29), 17 (range, 10 to 34), and 22 (range, 10 to 35). In other words, all patients demonstrated worsening hepatic function post-TIPS.

Renal replacement therapy

Seven of 18 patients (39%) required hemodialysis before TIPS. All seven had undergone TIPS for refractory ascites. Of the 11 patients who did not require renal replacement therapy before TIPS, none required renal replacement therapy after TIPS.

Because this was a retrospective review and medical records were often incomplete, the presence and degree of encephalopathy could not be determined for the pretransplantation, pre-TIPS, or post-TIPS periods. In addition, many patients were critically ill, often with sepsis, multisystem organ failure, or both. So mental status decline was difficult to determine and impossible to attribute to ESLD in many patients. As such, serum ammonia levels were used as surrogate measures for encephalopathy. Median overall values for the pre- and post-TIPS periods were 27 μmol/L (range, 12 to 87 μmol/L) and 51 μmol/L (range, 30 to 123 μmol/L), respectively; median peak values were 52 μmol/L (range, 12 to 295 μmol/L) and 112 μmol/L (range, 51 to 378 μmol/L), respectively.

At last followup, 6 patients (33%) underwent retransplantation; 12 (67%) did not. Median time to retransplantation was 58 days (range, 2 to 71 days) post-TIPS. For patients not undergoing retransplantation, median overall survival was 95 days (range, 13 to 1,400 days). Three nonretransplanted patients (25%) were alive and well at a median of 90 days (range, 78 to 1,169 days) post-TIPS. Nine patients not having retransplantation (75%) had died at a median of 99 days (range, 13 to 1,400 days) post-TIPS. The most common causes of death were ESLD and sepsis.

The majority of the study population had TIPS placed for refractory ascites (16 of 18 patients, 89%); this subgroup was further scrutinized (Table 2). Of 16 patients, 8 (50%) were responders and 8 (50%) were nonresponders. Responders demonstrated no further need for paracenteses and reduction of ascites on post-TIPS ultrasound or CT. Nonresponders did not achieve one or both of the criteria. Although statistical analyses failed to demonstrate statistically significant differences, compared with nonresponders, responders were younger, more likely to have been transplanted for HCV cirrhosis, had higher median pre-TIPS portal pressures, had greater median reductions in portosystemic pressure gradients, had less immediate post-TIPS coagulopathy, and were more likely to survive longterm. All nonresponders who did not undergo retransplantation died at a median of 31 days (range, 13 to 946 days) post-TIPS (Table 2).

Two patients who had presented with variceal bleeding were not included in this majority subgroup analysis. One of them, a 63-year-old man who was 6.5 years status-post-deceased-donor liver transplant, was diagnosed with recurrent HBV infection and cirrhosis. He presented with hematemesis and was found to have esophageal and gastric varices. He successfully underwent TIPS placement, with a reduction in portal pressure of 3 mmHg (12%) and a reduction in portosystemic pressure gradient of 5 mmHg (38%). He was alive and well with no recurrent bleeding at 78 days post-TIPS. But his serum INR, creatinine, bilirubin, and MELD score increased. Despite worsening renal

Table 2. Comparison of Patients Whose Postliver Transplant Refractory Ascites Did and Did Not Respond to Transjugular Intrahepatic Portosystemic Shunt

Characteristic	Responders (n = 8)	Nonresponders (n = 8)	p Value
Men, n (%)	6 (75)	6 (75)	> 0.99
Median age, y (range)	49 (47–53)	55 (42–63)	0.14
Etiology of pretransplant ESLD, n (%)			
HCV	8 (100)	4 (50)	0.08
EtOH	0 (0)	3 (38)	0.20
Sarcoidosis	0 (0)	1 (13)	> 0.99
Donor type, n (%)			
Deceased	8 (100)	7 (88)	> 0.99
Live	0 (0)	1 (13)	> 0.99
Days from transplant to TIPS, median (range)	918 (287–2,853)	1,188 (209–3,415)	0.55
Portal pressure, median (range)			
Pre-TIPS pressure, mmHg	24 (19–29)	20 (17–25)	0.16
Post-TIPS pressure, mmHg	16 (15–18)	15 (11–19)	0.37
Absolute reduction in pressure, mmHg	9 (3–11)	6 (1–11)	0.43
Relative reduction in pressure, %	38 (15–41)	26 (5–50)	0.72
Portosystemic venous pressure gradient, median (range)			
Pre-TIPS pressure gradient, mmHg	21 (8–24)	14 (11–22)	0.29
Post-TIPS pressure gradient, mmHg	8 (2–12)	7 (5–10)	0.39
Absolute reduction in pressure gradient, mmHg	13 (6–16)	8 (5–12)	0.13
Relative reduction in pressure gradient, %	62 (43–75)	55 (38–64)	0.14
Serum laboratory values, median (range)			
Baseline albumin, g/dL	2.7 (1.6–3.6)	2.5 (1.6–3.0)	0.29
Baseline INR	1.2 (1.0–1.4)	1.2 (1.0–1.6)	0.89
Immediate post-TIPS INR	1.3 (1.0–1.7)	1.5 (1.1–2.0)	0.10
Longterm post-TIPS INR	1.2 (1.0–1.9)	1.3 (1.1–2.0)	0.38
Baseline creatinine, mg/dL	1.8 (1.4–3.5)	2.2 (1.8–4.9)	0.42
Immediate creatinine, mg/dL	1.6 (0.9–3.9)	1.9 (1.5–5.1)	0.52
Longterm creatinine, mg/dL	1.8 (0.7–8.1)	1.9 (1.2–3.7)	0.57
Baseline bilirubin, mg/dL	1.2 (0.2–4.5)	0.6 (0.4–26.7)	0.48
Immediate post-TIPS bilirubin, mg/dL	2.1 (0.3–9.1)	1.0 (0.5–27.6)	0.50
Longterm post-TIPS bilirubin, mg/dL	1.6 (1.3–8.3)	1.8 (0.8–29.8)	0.38
Pre-TIPS ammonia, μmol/L	28 (24–87)	32 (12–43)	0.93
Post-TIPS ammonia, μmol/L	64 (46–92)	51 (30–123)	0.54
Peak pre-TIPS ammonia, μmol/L	47 (27–295)	63 (12–85)	0.53
Peak post-TIPS ammonia, μmol/L	132 (88–378)	90 (55–220)	0.69
Renal replacement therapy, n (%)			
Pre-TIPS	5 (63)	2 (25)	0.31
Post-TIPS	5 (63)	2 (25)	0.31
MELD score, median (range)			
Baseline score	16 (12–29)	17 (16–25)	0.59
Immediate post-TIPS score	15 (10–34)	22 (14–29)	0.24
Longterm post-TIPS score	23 (10–35)	20 (11–30)	0.76
Clinical outcomes			
Retransplant, n (%)	3 (38)	2 (25)	> 0.99
Post-TIPS days to retransplant, median (range)	67 (59–71)	39 (21–57)	
Alive and well without retransplant, n (%)	2 (40)	0 (0)	0.18
Post-TIPS days alive and well without retransplant, median (range)	493 (90–1,169)	None	
Post-TIPS days to death without retransplant, median (range)	200 (94–1,400)	31 (13–946)	0.27

ESLD, end-stage liver disease; EtOH, ethanol; HCV, hepatitis-C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunts.

function after TIPS, he did not require renal replacement therapy.

The second patient was a 16-year-old male adolescent with cystic fibrosis. He received a left lateral live-donor allograft. His postoperative course was complicated by small-for-size syndrome with associated venous congestion. Admitted to an ICU with multisystem organ failure, multisource septic shock, and profound anemia and coagulopathy, the patient also had had severe hematemesis. On endoscopy, the patient had esophageal and gastric varices. He underwent TIPS at 122 days post-transplant. This reduced his portal pressure by 38 mmHg (76%) and his portosystemic venous pressure gradient by 18 mmHg (60%). As with the previous patient, serum laboratory values demonstrated worsening hepatic and renal function (without the need for renal replacement therapy); the MELD score increased from 13 to 23. The patient survived to retransplantation at 26 days without recurrent bleeding in the interim. But shortly after retransplantation, the patient died of multisystem organ failure.

DISCUSSION

For liver-transplant recipients with recurrent ESLD and portal hypertension, clinicians should ask: "Can TIPS be placed and should TIPS be placed?" For the most part, the answer to the first part of the question has been determined. As previously and currently demonstrated, TIPS in the postliver-transplantation population are technically feasible, even in patients with segmental allografts.[14] Indeed, 18 of 19 patients in this study (95%) who presented for TIPS ultimately underwent successful placement. But this did not mean that such interventions were undertaken lightly or without difficulty. Although 95% of patients had successfully received TIPS, only 83% of patients underwent successful placement during the first attempt; the remainder (17%) underwent successful placement during the second attempt.

"Should TIPS be placed?" is a more complicated question. To answer it, one should consider whether the patients in question are candidates for retransplants and whether TIPS are bridges to retransplants or definitive therapies in and of themselves. If they are bridges, then TIPS may be acceptable as long as they do not complicate retransplantation. Indeed, this does not seem to be the case; quite simply, TIPS do not complicate transplantation and should not, for that matter, complicate retransplantation.[6,7] Six patients had successful retransplantation at a median of 58 days (range, 21 to 71 days). This was in accord with previous reports in which patients were retransplanted at 14 to 210 days.[10,12]

Because TIPS did not slow or stop the progression of ESLD, it was not unexpected that patients demonstrated unchanged or worsening hepatic function. Indeed, serum INR, creatinine, bilirubin, and MELD scores all increased post-TIPS. In this article, these increasing MELD scores seemed largely from worsening hepatic function (increasing serum bilirubin and INR) rather than worsening renal impairment. (TIPS was not associated with increasing serum creatinine levels or with new-onset need for renal replacement therapy; patients who did not need hemodialysis before TIPS did not need hemodialysis after TIPS.)

Because this study was retrospective, it was difficult to study the relationship between TIPS and encephalopathy. Nevertheless, it was clear that both overall and peak serum ammonia levels also increased post-TIPS. Although such physiologic decline was not necessarily problematic, at least immediately, for patients who were candidates for retransplant, for noncandidates, this carried the potential for continued and lifelong stigmata of disease and debilitation. Indeed, for noncandidates for retransplant, median survival was 95 days (range, 13 to 1,400 days) post-TIPS. These 13 to 1,400 days represented a period during which TIPS may or may not have controlled the symptoms of portal hypertension but during which disease progression was most certainly assured—a morbid prospect indeed.

So balance of the benefits and risks of TIPS for nonretransplant candidates must be considered; to place TIPS or not to place TIPS hinges on the efficacy of TIPS in controlling the symptoms for which they are used. In this article, for patients with GI bleeding, TIPS were clearly efficacious; both patients responded to TIPS and no further evidence of bleeding was seen in either patient. Other studies have concluded that TIPS were successful in 50% to 100% of patients with variceal bleeding ($n = 1$ to 6).[9-13] In addition, because of the potential for catastrophic hemorrhage, early and proactive intervention, first with endoscopic therapies and then with TIPS, seemed prudent.

For liver-transplant recipients with refractory ascites, the utility of TIPS was more limited. In this article, TIPS were successful in only 50% of patients. There were several possible reasons for this. First, criteria for response and nonresponse may have been too stringent. One criterion—no further need for paracenteses—seemed reasonable and necessary, particularly in light of the superiority of TIPS over repeated paracenteses for patients awaiting transplants, as demonstrated by a previous report.[3] The other criterion—reduction of ascites on post-TIPS ultrasound or CT—was perhaps excessively optimistic and possibly unrealistic. But according to Somberg and colleagues,[7] fewer instances of ascites were seen on laparotomy in patients with TIPS than without. So although patients may not require further paracenteses, it seemed acceptable to expect patients to demonstrate decreased ascites as well.

Another reason for the underwhelming response of refractory ascites to TIPS was perhaps manifest in portal and systemic pressure measurements and alterations. Although not statistically significant, responders tended to have greater median pre-TIPS portal pressures (21 mmHg [range, 8 to 24 mmHg] versus 14 mmHg [range, 11 to 22 mmHg]; $p = 0.16$). In addition, responders also showed greater reductions in portosystemic pressure gradients (median absolute reduction, 13 mmHg [range, 6 to 16 mmHg] versus 8 mmHg [range, 5 to 12 mmHg]; $p = 0.13$; median relative reduction, 62% [range, 43% to 75%] versus 55% [range, 38% to 64%]; $p = 0.14$). So it may have been the case that compared with nonresponders, responders had more severe portal hypertension pre-TIPS and more aggressive reductions in portosystemic pressure gradients post-TIPS—more to decompress and more that was decompressed. Of course, for nonresponders, TIPS could have been revised to increase portosystemic shunting, having more of the portal circulation bypass the hepatic parenchyma. But this may have induced worsening hepatic function and encephalopathy, because fewer nutrients and metabolic waste products reached even marginally functional hepatocytes. In addition, although TIPS accomplished substantial decompressions of the portal venous circulation, reducing median portal pressures from 22 mmHg (range, 17 to 50 mmHg) to 16 mmHg (range, 11 to 22 mmHg), patients still demonstrated portal hypertension post-TIPS, if not symptomatically at least numerically. Insofar as portal pressures ranging from 11 to 22 mmHg were pathologic, a high degree of nonresponse was perhaps not unexpected. Other studies have reported similar reductions and rates of response, ranging from 50% to 100% ($n = 5$ to 8).[9-13]

A third explanation for low response rates may have been that some patients had such poor physiologic function that control of refractory ascites would have been nearly impossible in the absence of significant portosystemic shunting. Nazarian and associates[17] reported that baseline hepatic and renal function predicted the success of TIPS in controlling refractory ascites in the preliver-transplantation population. They demonstrated that a baseline serum bilirubin of less than 3.0 mg/dL and a baseline serum creatinine level of less than 1.9 mg/dL were independent predictors of the ability of TIPS to control refractory ascites in the long-term. On one hand, in this article, both responders and nonresponders demonstrated median baseline serum bilirubin levels less than that established by Nazarian and coworkers[17] (1.2 mg/dL [range, 0.2 to 4.5 mg/dL] and 0.6 mg/dL [range, 0.4 to 26.7mg/dL], respectively). On the other hand, the responder group demonstrated median baseline creatinine levels less than that established by Nazarian and coauthors,[17] but the nonresponder group demonstrated median baseline creatinine levels that were greater (1.8 mg/dL [range, 1.4 to 3.5 mg/dL] and 2.2 mg/dL [range, 1.8 to 4.9 mg/dL], respectively). Unlike Nazarian and colleagues, we were unable to establish predictors for response and nonresponse of refractory ascites to TIPS. Nevertheless, in general, younger patients with greater pre-TIPS portal pressures and greater reductions in portosystemic pressure gradients tended to have more responsive ascites than their older, less portal hypertensive, less shunted counterparts.

In addition, the pathophysiology of ascites is not limited to portal hypertension. Portal hypertension, hyperdynamic cardiovascular systems, visceral vasodilation, renal insufficiency, sodium retention, hypoalbuminemia, and other factors all contribute to the development of refractory ascites. So although TIPS may achieve mechanical decompressions of the portal circulation, they cannot slow, stop, or resolve these other elements of ESLD. In fact, by bypassing the liver parenchyma, these elements may worsen. Because of the multifactorial pathophysiology of ascites, it was perhaps not surprising that no single factor was clearly and unequivocally associated with the response or nonresponse of refractory ascites to TIPS. In a sense, ESLD is a disease with effects outside of the hepatic parenchyma, with effects throughout the body. So overall clinical pictures, not simply the portal pressures, determined whether ascites developed and whether they became refractory to single or multiple treatment modalities.

Again: Can and should TIPS be placed in liver-transplant recipients? The answer to the first part is a resounding yes. The answer to the second part is perhaps. Indeed, the balance of benefit and risk of TIPS in liver-transplant recipients with refractory ascites was tenuous at best, for TIPS did not stop or slow the progression of ESLD and offered symptomatic relief in only 50% of patients. Additionally, all nonresponders who were not candidates for retransplantation (6 of 6 patients) died at a median of 31 days (range, 13 to 946 days). (In comparison, 60% of responders who were not candidates for retransplantation [3 of 5 patients] died at a median of 200 days [range, 94 to 1,400 days]). In the absence of models for predicting response and nonresponse, transplant surgeons, gastroenterologists, and interventional radiologists must rely on their overall clinical impressions of patients on a case-by-case basis, taking ages, portal pressures, and baseline hepatic and renal functions into consideration. In addition, clinicians must determine whether patients would be able to tolerate the post-TIPS period, especially those who are not candidates for retransplant. But insofar as these patients represented a population with often debilitating symptoms and limited options, TIPS ought to be considered and attempted.

Even though this study was the largest and perhaps most comprehensive analysis of TIPS in liver-transplant recipients, its study population was small and its data were retrospective. Certainly, larger, multicenter, prospective, randomized studies are needed, especially as the population of liver-transplant recipients continues to grow. Future topics for study include the relationship between TIPS and immunosuppression, optimal timing of TIPS, and a clearer understanding of TIPS and encephalopathy.

In conclusion, the utility of TIPS in liver-transplant recipients was limited. For two patients, it prevented repeated variceal bleeding. For 16 patients, refractory ascites responded to TIPS in 50% of cases; post-TIPS, 50% of patients either required further paracenteses or did not demonstrate resolving or resolved ascites on ultrasound or CT. Because no clear and convincing factor was associated with response or nonresponse of refractory ascites to TIPS, clinicians must determine whether TIPS are warranted on a case-by-case basis, taking the overall clinical picture into account.

Author Contributions

Study conception and design: Choi, Jain
Acquisition of data: Choi, Jain
Analysis and interpretation of data: Choi, Jain
Drafting of manuscript: Choi, Jain, Orloff
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REFERENCES

1. Rösch J, Hanafee WN, Snow H. Transjugular portal venography and radiologic portacaval shunt: an experimental study. Radiology 1969;92:1112–1114.
2. Richter GM, Palmaz JC, Noldge G, et al. The transjugular intrahepatic portosystemic stent-shunt. A new nonsurgical percutaneous method. Radiologe 1989;29:406–411.
3. Rössle M, Ochs A, Gülberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–1707.
4. LaBerge JM, Somberg KA, Lake JR, et al. Two years outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: results in 90 patients. Gastroenterology 1995;108:1143–1151.
5. Richard HM, Cooper JM, Ahn J, et al. Transjugular intrahepatic portosystemic shunts in the management of Budd-Chiari Syndrome in the liver transplant patient with intractable ascites: anatomic considerations. J Vasc Interv Radiol 1998;9:137–140.
6. Lerut J, Laterre PF, Goffette P, et al. Transjugular intrahepatic portosystemic shunt and liver transplantation. Transpl Int 1996; 9:370.
7. Somberg KA, Lombardero MS, Lawlor SM, et al. A controlled analysis of the transjugular intrahepatic portosystemic shunt in liver transplant recipients. Transplantation 1997;63:1074–1079.
8. The United States Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients Annual Report 2007. United States Department of Health and Human Services. Available at: http://www.optn.org/AR2007/default.htm. Accessed August 1, 2008.
9. Kim JJ, Dasika NL, Yu E, et al. Transjugular intrahepatic portosystemic shunts in liver transplant recipients. Liver Int 2008; 28:240–248.
10. Amesur NB, Zajko AB, Orons PD, et al. Transjugular intrahepatic portosystemic shunt in patients with who have undergone liver transplantation. J Vasc Interv Radiol 1999;10:569–573.
11. Lerut JP, Goffette P, Molle G, et al. Transjugular intrahepatic portosystemic shunt after adult liver transplantation: experience in eight patients. Clin Transplant 1999;68:379–384.
12. Van Ha TG, Funaki BS, Ehrhardt J, et al. Transjugular intrahepatic portosystemic shunt placement in liver transplant recipients: experiences with pediatric and adult patients. Am J Roentgenol 2005;184:920–925.
13. Abouljoud M, Yoshia A, Kim D, et al. Transjugular intrahepatic portosystemic shunts for refractory ascites after liver transplantation. Transplant Proc 2005;37:1248–1250.
14. Saad WEA, Davies MG, Lee DE, et al. Transjugular intrahepatic portosystemic shunt in a living donor left lateral segment liver transplant recipient: technical considerations. J Vasc Interv Radiol 2005;16:873–877.
15. Schemmer P, Radeleff B, Flechtenmacher C, et al. TIPSS for variceal hemorrhage after living related liver transplantation: a dangerous indication. World J Gastroenterol 2006;12:493–5.
16. Senzolo M, Patch D, Cholongitas E, et al. Severe venoocclusive disease after liver transplantation treated with transjugular intrahepatic portosystemic shunt. Transplantation 2006;82:132–135.
17. Nazarian GK, Bjarnason H, Dietz GA, et al. Refractory ascites: midterm results of treatment with a transjugular intrahepatic portosystemic shunt. Radiology 1997;205:173–190.