

Does advanced chronic kidney disease impact transjugular intrahepatic portosystemic shunt efficacy and safety?

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Abstract

Background and study aims : There are currently limited data available summarizing the clinical outcomes and safety of transjugular intrahepatic portosystemic shunts (TIPS) in cases of advanced chronic kidney disease (CKD). The study aimed to assess efficacy and safety of TIPS in patients with advanced CKD.

Patients and methods : Seventeen patients (M:F 8:9, age 55 years, MELD 24) with grade 4-5 CKD who underwent TIPS for ascites (n = 7) or varices (n = 10) were analyzed. The primary outcome was TIPS efficacy – assessed by comparing paracentesis frequency and diuretic regimen pre- and post-TIPS among ascites patients – and through bleeding cessation in variceal bleeding patients. Other outcomes included hepatic encephalopathy (HE), GFR increase, and mortality.

Results : Median baseline GFR was 19.9 mL/min. No patients were hemodialysis dependent. Median post-TIPS pressure gradient was 8 mm Hg. Among ascites patients, 5/6 (83%) were TIPS responsive, with reduced or stable diuretics in 4/5 (80%). Among variceal hemorrhage cases, bleeding cessation rate was 90% (9/10). New or worsening HE incidence was 47% (8/17), and one patient required shunt reduction. Of 8 patients with lab follow-up, 6 (75%) demonstrated significant GFR increase (42.2 versus 20.0 mL/min, P = 0.028). The 90-day mortality incidence was 29% (5/17).

Conclusions : In conclusion, TIPS can potentially address ascites and variceal bleeding in advanced CKD patients, though HE incidence may be increased. Further investigation in larger cohorts may corroborate these results. (*Acta gastroenterol. belg.*, 2017, 80, 243-248).

Key words : Chronic kidney disease (CKD) ; Transjugular intrahepatic portosystemic shunt (TIPS) ; safety ; efficacy.

Introduction

Over the last 25 years, transjugular intrahepatic portosystemic shunt (TIPS) creation has been established as an essential component in the clinical care of patients with liver cirrhosis and complications of portal hypertension (1). To this end, TIPS has proven an effective treatment for medically refractory ascites and recurrent or resistant variceal hemorrhage, with clinical efficacy rates reaching 90% (2, 3). While TIPS has been successfully employed for these conditions in the setting of mild to moderate comorbid renal insufficiency (4), advanced chronic kidney disease (CKD) may theoretically diminish TIPS effectiveness. From the standpoint of ascites, patients with CKD have an inherently impaired natriuretic capacity that results in compromised diuresis and the potential for persistent ascites despite enhanced post-TIPS renal perfusion that typically increases sodium

excretion and fluid diuresis (5). In the context of variceal bleeding, CKD patients suffer from dysfunctional platelet aggregation that is associated with prolonged bleeding times (6) and which may theoretically potentiate more significant bleeding events in the face of variceal flow diversion. In all such advanced CKD patients, TIPS may also increase the risk for hepatic encephalopathy (HE) due to diminished capability for renal ammonia excretion. To date, there are limited explicit data available summarizing the clinical outcomes and safety of TIPS in cases of advanced CKD (7), which may prompt empiric avoidance of TIPS in the setting of this purported relative contraindication. With this in mind, the current study was undertaken to investigate the clinical efficacy and safety of TIPS creation for both ascites and variceal bleeding in the context of advanced CKD.

Materials and methods

Clinical setting and patients

The patient cohort for this study were selected from a registry of 302 patients who underwent 305 technically successful TIPS procedures between November 1998 and December 2014 in the Division of Interventional Radiology at an academic tertiary care medical center. Patients with advanced, stage 4 or 5 CKD (n = 17/302, 6%) – defined by a glomerular filtration rate (GFR) measuring less than 30 mL/min based on the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation present for three or more months (Table 1) (8) – were extracted from this registry for further investigation. Patient GFRs were calculated within the electronic medical record using the Modified Diet in Renal Disease (MDRD) equation (9). The identified patients were stratified into two cohorts based on their primary indication for TIPS, either refractory ascites (n = 7) or variceal hemorrhage (n = 10).

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Table 1. — KDOQI stages of kidney disease

Stage	GFR (mL/min) ^a	Description
1	≥ 90	Normal or increased GFR
2	60-89	Mildly decreased GFR
3	30-59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	< 15 or dialysis dependent	Kidney failure

KDOQI = Kidney Disease Outcomes Quality Initiative, GFR = glomerular filtration rate ^a All GFR values are normalized to an average body surface area of 1.73 m²

Patients were also further separated based on clinically suspected CKD etiology, either functional impairment from hepatorenal syndrome (HRS) versus other organic medical causes such as diabetes mellitus, hypertension, or drug toxicity. Baseline patient characteristics are summarized in Table 2.

TIPS procedures

The technique for TIPS creation—which were performed by seven Certificate of Added Qualification (CAQ) accredited Interventional Radiologists (IRs) with 2 years to more than 20 years of attending physician experience—has been previously described (10, 11). Shunts were created using either a 10 mm Viatorr stent-graft (W. L. Gore & Associates, Flagstaff AZ) (n = 14/17, 82%) or a 12 mm Wallstent (Boston Scientific, Natick MA) (n = 3/17, 18%). The target post-TIPS portosystemic pressure gradient (PSG) was less than 12 mm Hg for both ascites and variceal hemorrhage patients (2), with hemodynamic success defined as PSG reduction meeting this threshold. TIPS were generally incrementally dilated after deployment utilizing an 8 mm balloon first, with further dilation using a 10 mm balloon to reduce PSG below 12 mm Hg if necessary. Embolization of gastroesophageal varices was performed

Table 2. — Study population features

Measure	Ascites cohort ^a		VH cohort ^a	
Number	7		10	
Age (years)	55 (44-65)		55 (38-71)	
Gender				
Male	4	(57%)	4	(40%)
Female	3	(43%)	6	(60%)
Ethnicity				
Caucasian	2	(29%)	6	(60%)
Hispanic	4	(57%)	4	(40%)
African-American	1	(14%)	0	(0)%
Liver disease etiology				
Alcohol	3	(30%)	2	(30%)
HBV or HCV	2	(30%)	4	(30%)
Alcohol and HBV or HCV	0	(0%)	1	(20%)
Other ^b	2	(20%)	3	(20%)
Pre-TIPS GFR (mL/min/1.73 m ²)	24.5 (17.9-29.6)		15.5 (5.2-20.1)	
MELD score	22 (19-28)		29.5 (19-40)	
Bilirubin (mg/dL)	1.8 (0.8-3.4)		3.3 (0.6-16.5)	
INR	1.5 (1.3-1.9)		1.5 (1.1-11.7)	
Creatinine (mg/dL)	2.4 (2.0-4.2)		3.7 (2.5-7.7)	
Child-Pugh score	10 (9-12)		9	(7-14)
Class A	0	(0%)	0	(0%)
Class B	5	(71%)	4	(40%)
Class C	2	(29%)	6	(60%)
HE history				
Yes	5	(71%)	4	(40%)
No	2	(29%)	6	(60%)

VH = variceal hemorrhage, HBV = hepatitis B virus, HCV = hepatitis C virus, GFR = glomerular filtration rate, MELD = Model for End-stage Liver Disease, INR = international normalized ratio,

^a Values reported as median (range) or number (percent)

^b Includes non-alcoholic steatohepatitis (NASH) and auto-immune hepatitis

following TIPS creation at the discretion of the primary operating IR based on clinical circumstance and imaging findings during TIPS creation.

Medical record review

The electronic medical record was reviewed by a medical student research associate or Radiology resident physician under the supervision of a CAQ-licensed IR with 8 years of attending physician experience to collect clinical, laboratory, procedure, and outcome data. HE was categorized according to the West-Haven classification scheme (12). Adverse events were graded according to the Society of Interventional Radiology classification of complications (13). Patient mortality was identified through electronic medical record review and was confirmed using the United States Social Security Death Index.

Measured outcomes

The primary outcome measure of this study was TIPS clinical efficacy. For the ascites cohort, TIPS effectiveness was measured by ascites control assessed by comparing the number of therapeutic paracentesis procedures required and performed during the 3-6 month periods before and after TIPS creation (10, 14), along with diuretic regimens before and after TIPS. Efficacy was classified as complete response (CR), characterized by no further paracentesis procedures necessitated after TIPS, partial response (PR), defined by a decrease in number of paracentesis procedures after TIPS, or non-response (NR), evidenced by no change or an increase in number of paracentesis procedures post-TIPS. Objective response (OR) was defined as CR plus PR rates. For the variceal bleeding cohort, TIPS efficacy was determined by immediate post-TIPS bleeding cessation rates. Secondary outcomes measures included post-TIPS HE incidence and severity, changes in renal function before and after TIPS as measured by GFR, variceal rebleeding incidence, and 90-day all-cause mortality incidence.

Statistical analysis

Descriptive statistics were used to characterize features of the study population and TIPS procedures, with results presented as median (range). Comparisons of categorical and continuous data for patients were compared using the Pearson's Chi-squared test and the Wilcoxon signed-rank test. Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago IL), with P-values < 0.05 considered as significant.

Results

CKD measures

Median GFR was 19.9 (range 5.2-29.6) mL/min across patients with CKD stage 4 (n = 8) or CKD stage 5 (n = 9). Median GFR in ascites patients was 24.5 (range 17.9-29.6) mL/min, and median GFR in variceal

hemorrhage patients was 15.5 (range 5.2-26.5) mL/min. CKD was caused by HRS in 47% (8/17), and by other organic medical causes – including diabetes mellitus, hypertension, and drug toxicity – in 53% (9/17). Renal toxicity due to interferon therapy was attributed along with HRS in 1 patient. CKD causes were predominantly established by clinical suspicion, although 1/17 (6%) patients underwent biopsy to pathologically confirm diabetes mellitus as the etiology of CKD. Among the study sample, there were no functionally anephric, dialysis dependent patients at the time of TIPS creation.

TIPS procedures

All TIPS procedures were hemodynamically successful, with a median post-TIPS PSG of 7 (range 5-11) mm Hg and 8.5 (range 2-12) mm Hg in the ascites and variceal bleeding cohorts, respectively, decreased from median pre-TIPS PSGs of 20 (range 14-28) mm Hg and 19.5 (range 11-32) mm Hg in the ascites and variceal bleeding cohorts. Five of 10 (50%) patients in the variceal bleeding cohort underwent concurrent adjunctive variceal embolization. There were no cases of post-TIPS fluid overload, right heart failure, or pulmonary edema among patients in this series. The incidence of de novo or worsening HE post-TIPS was 8/17 (47%). HE grades spanned grades 1 (n = 3, 37.5%), 2 (n = 3, 37.5%), and 3 (n = 2, 25%). Seven cases (87.5%) of HE were controlled with medical therapy consisting of lactulose with or without rifaximin. One patient (12.5%) in the ascites cohort with post-TIPS grade 3 HE required shunt reduction at 16 days post-TIPS for medically recalcitrant HE, which resulted in symptom alleviation.

TIPS clinical efficacy

Ascites cohort among the ascites patients, 6/7 (86%) had adequate clinical follow-up (3-month follow-up in 2 and 6-month follow-up in 4) for outcome assessment; one patient underwent early liver-kidney transplantation 9 days post-TIPS. Diuretic regimen changes are summarized in Table 3. One of 6 (17%) had CR with stable diuretic needs, while 4/6 (67%) had PR with reduced (n = 2), stable (n = 1), or increased (n = 1) diuretic needs, and 1/6 (17%) had NR. OR rate post-TIPS was 83% (5/6). Changes in paracentesis requirements are shown in Figure 1. Although statistical significance was not reached, there was a meaningful decrease in the number of paracentesis procedures post-TIPS compared to pre-TIPS across the entire ascites cohort (median 7, range 0-8 versus median 2, range 2-23; P = 0.068), with the median change being a decrease by 5 (range -15 to 0) procedures.

Variceal hemorrhage cohort

Among variceal bleeding cases, the immediate bleeding cessation rate was 9/10 (90%). One of 10 (10%) patients suffered from persistent bleeding and hemorrhagic shock after emergent, rescue TIPS creation. Rebleeding

Table 3. — Summary of diuretic changes before and after TIPS

Case	CKD cause	Pre-TIPS diuretics	Post-TIPS diuretics	Diuretics
1	HRS	None	F 60 mg QD	Increased
2	HRS	F 40 mg QD	F 40 mg QD	Even
3	DM, HTN	F 40 mg BID	F 40 mg BID	Even
4	HTN	F 80 mg QD, S 100 mg TID	F 40 mg QD, S 100 mg QD	Reduced
5	HRS, DM	F 20 mg QD	None	Reduced
6	HRS	F 40 mg QD	None	Reduced
7	HTN	F 40 mg BID, S 50 mg QD	a	a

TIPS = transjugular intrahepatic portosystemic shunt, CKD = chronic kidney disease, HRS = hepatorenal syndrome, HTN = hypertension, DM = diabetes mellitus, F = furosemide, S = spironolactone

^a Patient underwent early post-TIPS liver transplant

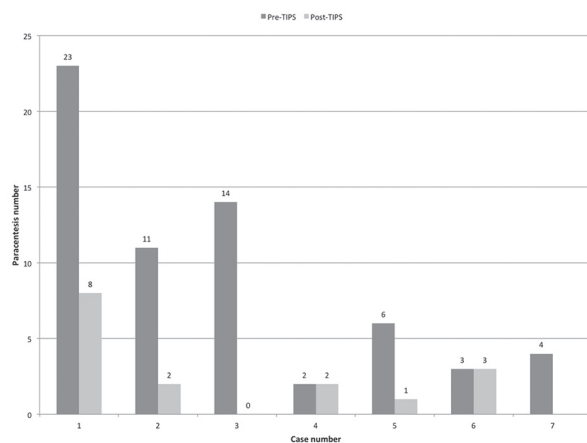


Figure 1. — Summary of paracentesis requirements before and after TIPS. Bar graphs show pre- and post-TIPS paracentesis number on per case basis. Cases 1-4 and 7 display data within 6-months pre- and post-TIPS, while cases 5-6 display data within 3-months pre- and post-TIPS. Of note, patient in case 7 underwent early post-TIPS liver transplant, resulting in no post-TIPS data

Table 4. — Summary of variceal hemorrhage clinical outcomes

Case	CKD cause	Post-TIPS rebleeding
1	HTN, DM	No rebleeding
2	HRS	No rebleeding
3	HRS	No rebleeding
4	HRS, DI	No rebleeding
5	HTN	No rebleeding
6	HRS	No rebleeding
7	HRS	No rebleeding
8	DM	No rebleeding
9	HTN, DM	No rebleeding
10	DM	< 24 hours

CKD = chronic kidney disease, TIPS = transjugular intrahepatic portosystemic shunt, HTN = hypertension, DM = diabetes mellitus, HRS = hepatorenal syndrome, DI = drug induced

outcomes are summarized in Table 4. For the remaining variceal hemorrhage patients, 4 patients remain alive (2 after liver transplantation) without rebleeding at the time of manuscript composition, and 5 patients died from causes unrelated to variceal hemorrhage, with no evidence for variceal rebleeding.

Renal function changes

Two of 17 patients, both from the variceal hemorrhage cohort, died within 24 hours of TIPS creation and did not have post-TIPS GFR information. Of the remaining 15, there was a significant increase in median GFR immediately (within 24 hours) post-TIPS (19.9 versus 21.7, $P = 0.02$), although this change was not clinically meaningful.

Short-term changes in GFR are shown in Figure 2. Eight of 15 (60%) individuals had lab follow-up between 3-12 months post-TIPS (1 at 3-months, 2 at 10-months, and 5 at 1-year), and 6/8 (75%) demonstrated a statistically significant increase in GFR when compared to baseline with median GFR 42.2 (range 31.8-85.9) mL/

min versus 20.0 (range 5.2-29.6) mL/min ($P = 0.028$). Two of 8 (25%) patients had trivial change in GFR from baseline at 1-year post-TIPS (-2.2 and +1.5 mL/min).

Mortality outcomes

The 90-day all-cause mortality incidence post-TIPS was 29% (5/17), a rate consistent with reported mortality rates for patients with Model for End-stage Liver Disease (MELD) scores in the range exhibited by the cohort herein (15). Mortality incidences at 90-days were 14% (1/7, patient expired after early liver-kidney transplant 9-days post-TIPS) and 40% (4/10) in the ascites and variceal hemorrhage cohorts, respectively. Two patients in the ascites cohort underwent liver transplantation- one with concurrent renal transplant-within 1-year post-TIPS. Two patients in the variceal hemorrhage also underwent liver transplant within 1-year post-TIPS.

Discussion

The results of this retrospective case series indicate that TIPS can potentially address ascites and variceal

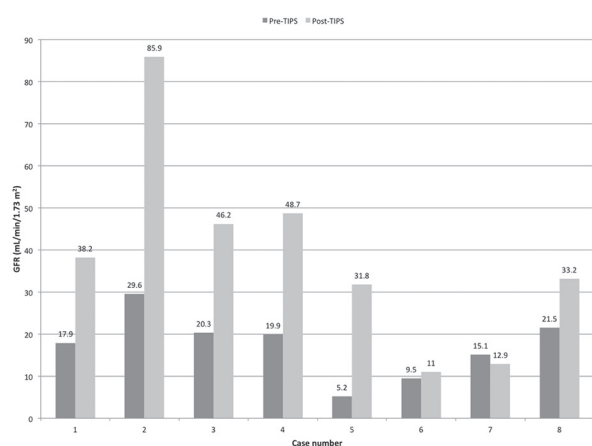


Figure 2. — Summary of GFR changes before and after TIPS. Bar graphs show pre- and post-TIPS GFR at 3-12 months post-TIPS among 8 patients with available lab data. First four cases are from ascites cohort, and last four cases are from variceal hemorrhage cohort.

bleeding in cirrhotic patients with concomitant advanced, stage 4 or 5 CKD. To this end, the majority of patients in this case series experienced clinical benefit from TIPS: 83% of ascites patients demonstrated partial or complete response to treatment, with an improvement in fluid retention as measured by an overall decrease in number of therapeutic paracentesis procedures, while 90% of variceal bleeding patients showed termination of hemorrhage after TIPS. The findings of the current series support the limited efficacy results described in 6 end-stage or advanced renal disease patients by Haskal and Radhakrishnan (7), all of whom showed clinical improvement in ascites when present along with variceal hemorrhage cessation without rebleeding. In all, our results suggest that the effectiveness of TIPS may not be dampened in patients with functional renal deficiency, and such individuals appear to express an appropriate physiologic response to portal decompression, namely mobilization of third space fluids. This outcome suggests that both IR and Hepatology practitioners may consider prescribing and applying TIPS in this distinctive patient population with potential for therapeutic value, despite an inherently impaired natriuretic capacity that may theoretically result in compromised diuresis or prolonged bleeding.

Despite advanced CKD standing, patients in the current series demonstrated renal functional improvement at 3-12 months post-TIPS across both HRS and other organic medical causes of renal disease, corroborating similar outcomes previously described in prior studies. In 2000, Brensing et al reported on 41 consecutive patients with advanced cirrhosis, refractory ascites, and renal insufficiency caused by HRS, 31 of whom subsequently underwent TIPS creation between 1995-1998 (16). Patients had a mean pre-TIPS creatinine clearance of 18 ± 15 mL/min, and showed significant improvement to 44 ± 28 mL/min at 1-month post-TIPS. The authors also found ascites improvement in 14 patients (45%) and complete

resolution in 10 (32%). In a small study by Michl et al published in 2000, 10 patients with mildly impaired renal function (serum creatinine > 1.5 mg per 100 mL) due to either HRS or organic renal disease underwent TIPS for medically refractory ascites between 1994-1999. These patients showed serum creatinine improvement from 1.8 ± 0.1 to 1.5 ± 0.1 mg/100 mL ($P < 0.05$) (17), and TIPS creation resulted in ascites reduction in 8 patients (4/6 with functional renal impairment, 4/4 with organic renal impairment) at a constant diuretic dosage (17). In 2004, Wong et al described significant improvement in renal function in 5 HRS patients who underwent TIPS after a refractory treatment response to oral midodrine, intravenous octreotide, and intravascular albumin, with return of almost normal GFR at 12-months post-procedure (18). In 2010, Anderson et al reported improvement in mean creatinine in 129 CKD patients (including 16 with CKD stage 4) treated with TIPS between 2001-2007, with those with worse baseline creatinine showing a more vigorous post-TIPS improvement (4). The outcomes of the current series similarly favor temporal post-TIPS improvement in renal function—which occurs secondary to enhanced post-TIPS renal perfusion—even in patients with organic causes of renal insufficiency, although definitive distinction from HRS is not likely not entirely possible.

The incidence of de novo or worsening post-TIPS HE in the advanced CKD cohort reported herein was 47%, which is relatively higher than the incidence of new or aggravated HE across published series, which ranges from 20-30% (19-21). This incidence also exceeds the frequency of de novo or worsening HE previously reported among all TIPS patients at our institution, which approximates 30% (22). This increased HE rate has its basis in the critical role played by the kidney in ammonia homeostasis, in that the decreased renal ammonia production and increased renal ammonia clearance typically seen in the context of portosystemic shunting (23) may be blunted in the setting of chronic kidney disease. This issue may manifest as severe post-TIPS HE, as reported in the series of Haskal and Radhakrishnan (7), where all patients suffered grade 2 or 3 HE post-TIPS and 4/6 (67%) required shunt reduction. The HE outcomes in the current series were not as extreme; most HE cases were medically manageable, although our cohort differed from that of Haskal and Radhakrishnan in that no patients herein were functionally anephric whereas most patients in the Haskal and Radhakrishnan cohort were dialysis dependent. Of note, 5 cases of grade 2 or 3 HE were encountered herein, and 1 patient did require shunt reduction. In all, these findings highlight the need for careful counseling of CKD patients of HE risks in the setting of possible TIPS creation, a fact that is magnified in importance given that the presence of renal failure has recently been shown to potentiate mortality in patients with HE (24).

There are limitations to this study. First, this was a retrospective, single arm, observational case series

experience of a single institution, with a small sample size. Second, patient follow-up was heterogeneous, and individuals did not follow a standardized treatment or imaging follow-up protocol.

This case series builds on the limited reported data about TIPS outcomes in advanced CKD patients, and suggests that TIPS may be a treatment option for addressing medically refractory ascites and variceal bleeding in this patient population. While TIPS also appears to improve renal function in advanced CKD due to HRS and organic medical causes of renal disease, HE incidence may be increased compared to patients with intact renal function. Further investigation in larger cohorts may corroborate these results.

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