

Simultaneous Combined Transjugular Intrahepatic Portosystemic Shunt and Partial Splenic Embolization for Decompensated Cirrhosis

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hepatic encephalopathy (HE), and survival were evaluated. Model for end stage liver diseases (MELD) scores were calculated.

RESULTS: TIPS creation was successful in all patients. After the treatments, patients in group B had better hepatic synthetic function, increased levels of white blood cells (WBC), platelets (PLT), and hemoglobin(HGB), lower frequency of HE, lower overall and cirrhosis-related mortality than patients in group A ($P<0.05$), though the two groups had similar recurrent variceal bleeding frequency ($P>0.05$). Multivariate analysis showed that MELD scores, HE, and group were independent factors for overall and liver-related mortality at month 24 ($P<0.05$). No severe complications were observed in the two groups.

CONCLUSIONS: Simultaneous combined TIPS and PSE regimen improves hematologic parameters, prevents deterioration of liver function and coagulation function, reduces variceal bleeding and HE, thus reduces mortality.

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Key Words: Transjugular intrahepatic portosystemic shunt(TIPS); Partial splenic embolization(PSE); Decompensated cirrhosis; Portal hypertension

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Abbreviation

TIPS: transjugular intrahepatic portosystemic shunt; PSE: partial splenic embolization; HBV: hepatitis B virus; HCV: hepatitis C virus; ALB: serum albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHE: cholinesterase; TBIL: total bilirubin; DBIL: direct bilirubin; Cr: creatinine; TC: total cholesterol; PT: prothrombin

ABSTRACT

AIM: To evaluate the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) in combination with partial splenic arterial embolization (PSE) for cirrhotic patients with recurrent variceal bleeding and hypersplenism.

METHODS: Institutional review board approval was obtained; all patients provided informed consent. From January 2010 to December 2014, a total of 141 cirrhotic patients received TIPS alone(group A, $n=114$) and simultaneous combined TIPS and PSE(group B, $n=27$) for recurrent variceal bleeding and hypersplenism secondary to portal hypertension. The TIPS was created by using covered stents. All patients underwent embolotherapy via the jugular vein after TIPS implantation. Patients in group B ($n=27$) received simultaneous PSE after creation of TIPS. Biochemical tests, coagulation function, complete blood cell (CBC) counts, frequencies of recurrent variceal bleeding and

time; INR: international normalized ratio; WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; PLT: platelet; CTP: Child-Turcotte-Pugh score; MELD: model for end stage liver disease; HE: hepatic encephalopathy; RR: relative risk; CI: confidence interval; NS: not significant; DSA: digital subtraction angiography.

INTRODUCTION

Although transjugular intrahepatic portosystemic shunt (TIPS) has been proved to be an effective treatment for preventing variceal bleeding secondary to portal hypertension in cirrhosis^[1,2], the risk of hepatic encephalopathy(HE) greatly increases after TIPS placement, and the risk of recurrent variceal bleeding after TIPS placement remains an issue^[1,3]. Risk factors for recurrent bleeding include an insufficient decrease in portosystemic pressure gradient after TIPS creation alone^[4].

Partial splenic arterial embolization(PSE), which has been an established interventional approach for portal hypersplenism^[5,6], appears to be efficacious to in reducing episodes of variceal bleeding^[7,8], improving hematologic parameters^[9,10], enhancing hepatic protein synthesis^[11], and reducing severity of HE^[12]. Therefore, we hypothesized that concomitant PSE can further improve the clinical outcomes of cirrhotic patients who underwent TIPS placement. The efficacy and safety of this simultaneous combined therapy are discussed below.

METHODS

Subjects

This study was approved by our institutional ethics committee. The study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki. No potential conflicts of interest were disclosed. Between January 2010 and December 2014, a total of 174 consecutive patients with cirrhosis and gastroesophageal variceal bleeding proved by emergent gastroscopy were identified in this study. In total, we performed TIPS alone in 114 patients (group A, $n=114$), and simultaneous combined TIPS and PSE in 27 patients (group B, $n=27$) (Figure 1).

Therapeutic protocol

After their conditions were stabilized by medications, and / or endoscopic band ligation or sclerotherapy, a physician and a consulted interventional radiologist explained the benefits and risks of the procedures to each patient in view of their laboratory tests and computerized tomography portal venography (CTPV) reports, and determined whether a patient would receive either TIPS alone or

simultaneous TIPS and PSE after giving informed consent.

Indications for TIPS and PSE in our center were gastroesophageal variceal bleeding and severe hypersplenism with white blood cell (WBC) counts below $2 \times 10^9/L$ or platelet (PLT) counts below $30 \times 10^9/L$ secondary to portal hypertension in cirrhosis, respectively. Patients with severe pulmonary hypertension(mean pulmonary artery pressure >45 mmHg) or known cardiac dysfunction such as congestive cardiac failure and severe tricuspid regurgitation^[3], severely impaired liver fuction (e.g. total bilirubin above 5mg/dL, INR >2.0 , current HE grade 2 or chronic HE), concomitant active infection, progressive renal failure or other hematological diseases leading to thrombocytopenia were considered unfit for this treatment^[13].

After receiving TIPS, all patients were given prophylactic low molecular weight heparin 4,100 IU (GSK China investment co., LTD) Qd or Q12h subcutaneously for 5-7 days, thereafter all patients were orally given aspirin (Bayer Schering Pharma AG) 100 mg Qd or clopidogrel (Sanofi Pharma Bristol-Myers Squibb SNC) 75 mg Qd to prevent blockage of the shunt by thrombus. All patients were given oral fructose, intravenous ornithine aspartate as prophylactics for HE.

TIPS procedure

TIPS was carried out by two highly experienced interventional radiologists in our institution according to the method described by Rossle *et al*^[14]. RUPS 100 puncture kit (Cook Inc. Bloomington, IN, USA) and ePTFE-covered stent (Fluency stent graft, 8mm \times 60mm, Angiomed GmbH Co.subsidiary of C.R. Bard, Inc.)were used in all patients. A stent was inserted between the right hepatic vein and right portal vein depending on anatomical conditions. Dilated collaterals including short gastric vein, gastric coronary vein were embolized with spring coils of varying diameters (35-8/5mm, 35-10/5mm, 35-6/3mm, 35-5/3mm, 35-4/3mm Cook Inc., Bloomington, IN, USA) (Figure 2A).

PSE procedure

PSE was also carried out by the same interventional radiologists, according to the method described in previous studies^[8,15]. During the procedure, a 5.0-F RH or Yashiro catheter (Terumo, Tokyo, Japan) was used to demonstrate the distribution of splenic arteries and collateral circulation routes, and spring coils(18-6/2mm, 18-10/4mm, Cook Inc., Bloomington, IN, USA) were used to embolize branches of the splenic arteries with a splenic infarction ratio set at below 50% (Figure 2B).

Follow-up protocol

All patients were followed up in our center at the 1st month, 4th months, 10th months post-treatment, then at a 6-month interval or any time a patient felt unwell. During each visit, laboratory tests including complete blood count (CBC), lipid metabolism, liver, kidney and blood coagulate functions, levels of HBV-DNA or HCV-RNA, and radiologic examinations including CTPV and Collor Doppler Ultrasound(CDUS) for abdomen and TIPS were performed on each patient.

Statistical analysis

Bivariate analyses of continuous variables were performed using Student's *t*-test or the Wilcoxon rank-sum test depending on the distribution. Pearson chi-square test was used for bivariate analyses of dichotomous variables. We also analyzed the overall survival and cirrhosis-related mortality with Kaplan-Meier method and compared difference by log-rank test. We performed univariate and multivariate analyses using a Cox proportional hazard model. All data are

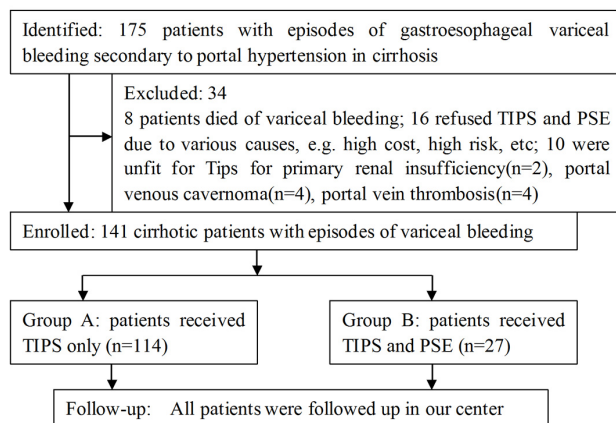


Figure 1 Patients disposition during the study.



Figure 2 A 52-year-old male cirrhotic patients with severe hypersplenism who had undertaken TIPS plus PSE. (A) Transjugular splenic portogram by DSA revealed that a shunt was established by implantation of a covered stent between the left main branch of portal vein and the middle hepatic vein and short gastric vein, gastric coronary vein were embolized with spring coils (B) Celiac angiogram after splenic embolization by DSA revealed obviously dilated and tortuous splenic artery, enlarged spleen and coil springs placed inside the distal splenic artery and its primary branches.

expressed as mean \pm standard deviation (SD). All *p* values were two-sided, and a *p* value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS package, version 13.0(SPSS Inc., Chicago, IL, USA).

RESULTS

Subjects characteristics

The baseline data, including age, gender, etiology, levels of red blood cell(RBC) counts and hemoglobin(HGB), liver function, coagulation function, Child classification and model for end stage liver disease (MELD) scores, positivities and levels of HBV-DNA and HCV-RNA, were comparable between the two groups ($P>0.05$), except that patients in group B had significantly lower levels of WBC and PLT($p<0.05$). (Table 1).

Changes of laboratory tests

Levels of WBC, HGB, PLT at pretreatment, at the 1st,4th, 10th month, 1.5 years, 2 years posttreatment are shown in Figure 3 a, b, and c. After the procedure, WBC, PLT counts, and HGB in group B increased significantly during the follow-up period compared to pretreatment levels ($P<0.05$). WBC counts in group B were similar at

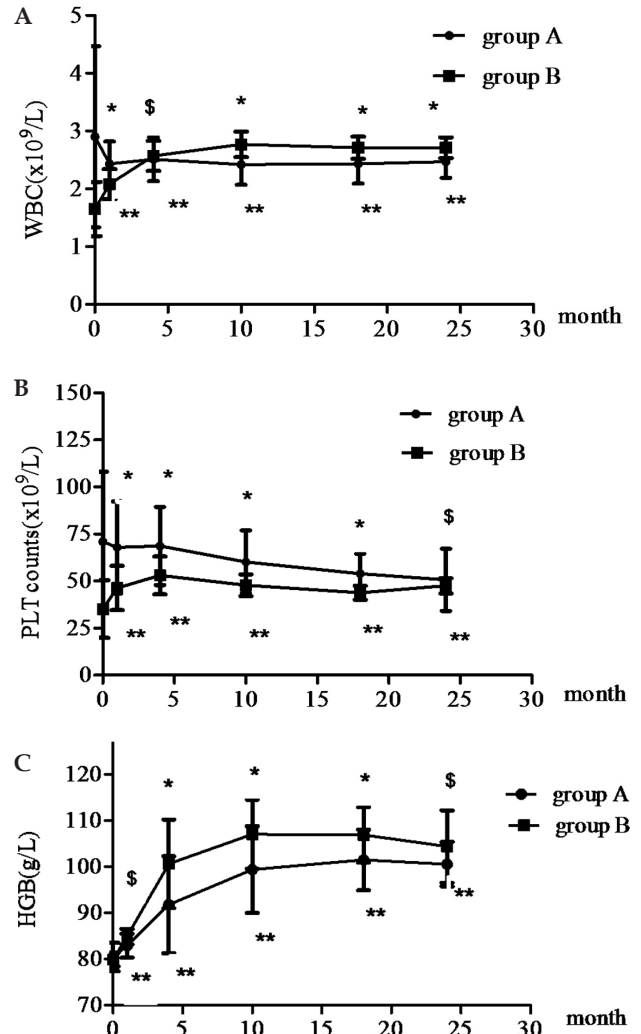


Figure 3 Serial change of WBC counts at different follow-up time point(month).\$ $p>0.05$,* $p<0.05$ when compared to group A at this point; ** $p<0.05$ when compared to pre-treatment count at this point in group B(a). Serial change of PLT counts at different follow-up time point(month).\$ $p>0.05$,* $p<0.05$ when compared to group A at this point; ** $p<0.05$ when compared to pre-treatment count at this point in group B(b). Serial change of HGB levels at different follow-up time point(month).\$ $p>0.05$,* $p<0.05$ when compared to group A at this point; ** $p<0.05$ when compared to pre-treatment count at this point in group A and B(c).

the 4th month ($P>0.05$) and higher than that of group A since the 10th month ($P<0.05$) forwards (Figure 3a). Despite being rising after PSE, PLT counts in group B were lower ($P<0.05$) than that of group A until 2 years posttreatment ($P>0.05$) (Figure 3b). After the procedures, HGB levels significantly increased in both groups($p<0.05$), though HGB in group B increased higher that of group A ($P<0.05$) (Figure 3c).

Laboratory tests, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (CHE), creatine (Cr),and levels of HCV-RNA were not significantly different between the two groups or within the two groups compared to pretreatment levels at each follow-up point ($P>0.05$, Table 2). However, serum albumin (ALB) levels increased significantly ($P<0.05$)in both groups compared to pretreatment levels, and ALB levels in group B were significantly higher than that in group A at every follow-up point ($P<0.05$, Table 2). Total cholesterol (TC) was similar between the two groups ($P>0.05$), while it increased significantly ($P<0.05$) in

group B since the 4th month forwards (Table 2). Total bilirubin(TBIL) increased significantly since the 4th month forwards in group A ($P<0.05$), but not in group B ($P>0.05$), and it remained significantly lower ($P<0.05$) in group B than that in group A since the 1st month forwards (Table 2). Prothrombin time (PT) increased significantly in group A ($P<0.05$) and it remained significantly higher than that of group B since the 4th month forwards (Table 2), though it increased in group B between the 4th and 10th month posttreatment, but normalized again since 1.5 years forwards. International normalized ratio(INR) in group A also escalated since 1st month ($P<0.05$) forwards, which remained significantly higher ($P<0.05$) than that in group B since the 10th month forwards, while it remained not significantly elevated until the 10th month posttreatment in group B (Table 2).

HBV-DNA in both groups decreased significantly since the initiation of antiviral therapy ($P<0.05$), and remained negative since the 4th month posttreatment in all HBV infected patients (Table 2).

Variceal bleeding and HE

Episodes of variceal bleeding in both groups reduced significantly ($P<0.05$) from 5.06 ± 2.22 to 0.076 ± 0.18 episodes per year in group A, and from 4.88 ± 1.96 to 0.063 ± 0.18 in group B (Figure 4a). HE increased significantly in group A from 0.18 ± 0.392 to 1.42 ± 0.71 episodes per year ($P<0.001$), but it remained similar in group B from 0.13 ± 0.35 to 0.38 ± 0.52 episodes per year ($P>0.05$, Figure 4b).

Predictive factors for mortality

In univariate analysis, pretreatment MELD score($P=0.000$), HE ($P=0.000$) were found to be significantly associated with overall and cirrhosis-related mortality (Table 3). In multivariate analysis, pretreatment MELD scores ($P=0.000$), HE ($P<0.01$) and group ($P<0.05$) were found to be independently associated with overall and cirrhosis-related mortality at month 24 (Table 3).

Overall mortality and cirrhosis-related mortality

By month 24, a total of 26 patients died of progression of hepatic cancer ($n=5$), sepsis ($n=2$), HE ($n=5$), hepatorenal syndrome ($n=4$), and liver failure ($n=10$), with 25 patients in group A and 1 in group B ($P=0.028$, Table 4). The one-year and 2-year overall survival rates were 93% and 78% in group A, 100% and 96% in group B. The mean overall survival time (SD) was 22.4 (0.38) months [95% Confidence Interval (CI): 21.6-23.1] in group A and 24.0 (0.02) months (95% CI: 23.9-24.0) in group B ($P=0.032$, log-rank test, Figure 5A). When only cirrhosis-related mortality was considered, mean survival time(SD) remained significantly longer in group B (Figure 5B, $p = 0.042$ by log-rank test).

Complications related to the interventional radiology technique

Almost all patients experienced nausea, dizziness after TIPS placement, however, severe complications such as gallbladder perforation, intraperitoneal haemorrhage, portal vein to bile duct fistula, localized collection between the gallbladder and the liver, pneumothorax, and neck haematoma, as reported in previous studies^[16,17], were not observed. Following PSE, 18 patients (66.7%) had mild fever(not above 38.5°C), abdominal pain and vomiting. No patients suffered splenic abscess, splenic rupture,pneumonia, refractory ascites, pleural effusions and gastrointestinal bleeding, as reported in previous studies^[18,19]. Patients in group B had similar hospital stays to that of group A ($P>0.05$, Table 4) in spite of additional intervention.

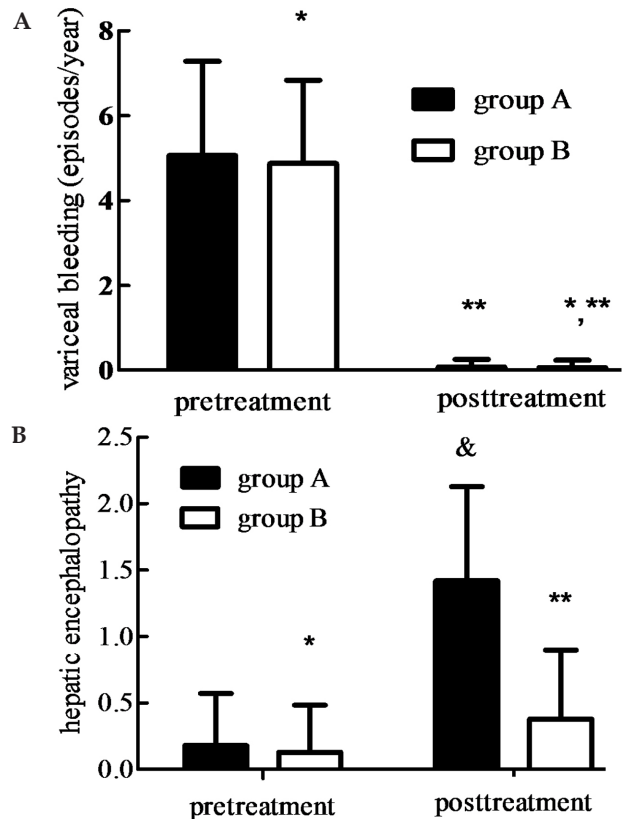


Figure 4 Gastroesophageal variceal bleeding before and after the treatments; * $p>0.05$, compared to group A; ** $p<0.001$, compared to group A and B in pretreatment(a). Hepatic encephalopathy before and after the treatments; * $p>0.05$, compared to group A; ** $p<0.001$, compared to group A in posttreatment ; & $p<0.001$, compared to group A in pretreatment(b).

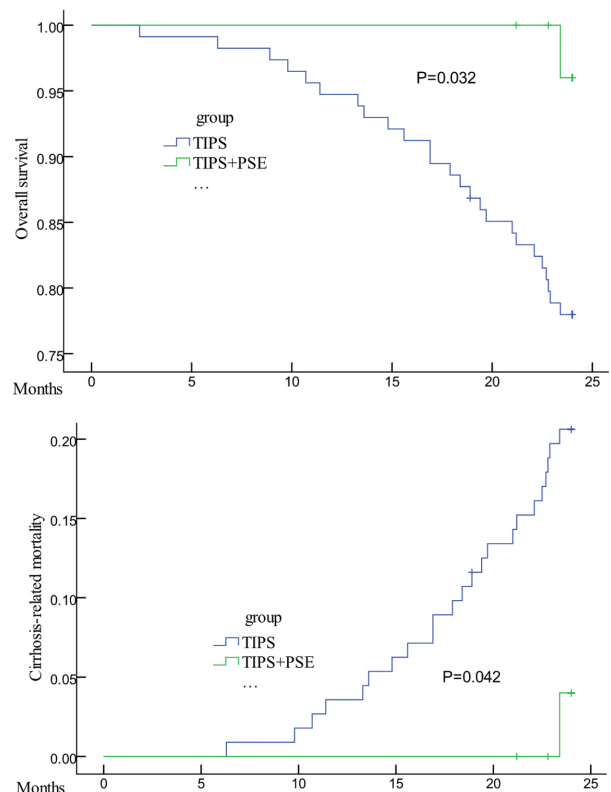


Figure 5 Kaplan-Meier analysis of time to overall mortality (A) and cirrhosis-related mortality (B) of patients treated with TIPS only (group A) and simultaneous TIPS and PSE (group B).

Table 1 Baseline characteristics of patients in group A and group B.

	Group A (n=114)	group B (n=27)	P value
WBC($\times 10^9/L$) [#]	2.90±1.57	1.65±0.47	*P=0.033
PLI($\times 10^9/L$) [#]	70.9±37.1	35.1±15.3	*P=0.012
Age, mean(SD)	50.1±11.0	49.4±9.9	*P=0.332
Gender			
Male, n(%)	78(68.4%)	17(63.0%)	**P=0.650
Etiology			
Hepatitis B, n(%)	96(84.2%)	24(88.9%)	
Hepatitis C, n(%)	9(7.9%)	2(7.4%)	**P=0.830
Alcoholic cirrhosis, n(%)	6(5.3%)	1(3.7%)	
PBC, n(%)	3(2.6%)	0(0%)	
RBC($\times 10^{12}/L$) [#]	2.88±0.08	2.85±0.07	*P=0.362
HGB(g/L) [#]	77.89±18.5	83.88±3.23	*P=0.371
ALT(U/L) [#]	28.8±24.7	24.1±10.2	*P=0.604
AST(U/L) [#]	45.0±24.2	35.9±11.6	*P=0.314
CHE(U/L)	2817.2±1071.8	2657.4±782.3	*P=0.695
Serum albumin(g/L)	26.2±1.47	27.0±1.7	*P=0.234
Total bilirubin (μmol/L)	31.9±25.2	26.3±7.4	*P=0.558
Direct bilirubin(μmol/L)	15.4±20.3	13.4±4.5	*P=0.785
Serum creatinine(μmol/L)	79.1±34.1	64.8±16.5	*P=0.257
Total cholesterol	2.70±0.83	2.37±0.23	*P=0.292
PT(second) [#]	20.2±2.8	21.6±2.5	*P=0.209
INR [#]	1.72±0.29	1.71±0.19	*P=0.782
CTP class	CTP class	CTP class	CTP class
Child A, n(%)	17(14.9%)	5(18.5%)	**P=0.859
Child B, n(%)	86(75.4%)	19(70.4%)	
Child C, n(%)	11(9.6%)	3(11.1%)	
CTP score [#]	8.52±1.09	8.88±1.13	*P=0.411
MELD [#]	10.9±0.93	11.33±0.68	*P=0.229
HBV DNA Positive, n(%)	47(49%)	11(45.8%)	**P=0.823
HBV DNA [#] , log (copies/mL)	8.5±8.2	3.66±1.29	*P=0.263
HCV RNA [#] , log (copies/mL)	5.25±1.04	5.27±1.00	*P=0.989

mean±SD; *P and **P was computed with Student's t-test and Pearson Chi-square test in SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

Table 3 Factors associated with overall and cirrhosis-related mortality at month 24.

Factors	Univariate analysis			Multivariate analysis		
	RR	95%CI	p	RR	95%CI	p
Overall mortality						
MELD	3.259	2.195-4.838	0.000	3.776	2.322-6.141	0.000
HE	5.317	2.406-11.753	0.000	5.223	1.793-15.214	0.002
group	0.151	0.020-1.111	0.063	0.059	0.005-0.764	0.030
Etiology	1.129	0.693-1.840	NS			
Age	0.962	0.914-1.012	NS			
Gender	0.587	0.202-1.705	NS			
ALB	0.931	0.722-1.202	NS			
ALT	1.008	0.933-1.023	NS			
AST	1.006	0.990-1.022	NS			
CHE	1.000	0.999-1.000	NS			
TBIL	1.003	0.989-1.017	NS			
Cr	1.000	0.979-1.042	NS			
TC	1.178	0.746-1.860	NS			
PT	1.001	0.871-1.151	NS			
INR	0.629	0.151-2.627	NS			
WBC	1.033	0.818-1.304	NS			
HGB	1.060	0.971-1.157	NS			
PLT	0.995	0.930-1.065	NS			
Cirrhosis-related mortality						
MELD	4.013	2.580-6.243	0.000			
HE	6.201	2.746-14.003	0.000			
group	0.162	0.022-1.201	0.075			
Etiology	0.939	0.512-1.721	NS			
Age	0.994	0.956-1.034	NS			
Gender	0.646	0.221-1.889	NS			
ALB	0.952	0.729-1.242	NS			
ALT	1.009	0.995-1.024	NS			
AST	1.005	0.989-1.022	NS			
CHE	1.000	0.999-1.000	NS			
TBIL	1.005	0.991-1.018	NS			
Creatine	0.994	0.966-1.023	NS			
TC	1.214	0.762-1.934	NS			
PT	1.025	0.889-1.182	NS			
INR	0.857	0.197-3.717	NS			
WBC	1.083	0.865-1.356	NS			
HGB	0.979	0.913-1.050	NS			
PLT	1.002	0.991-1.012	NS			

p was computed with Cox-proportional hazard model in SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

Table 2 Laboratory tests of patients in two groups during the 2- year follow-up.

Variables	Pre-treatment	1stmonth	4thmonth	10thmonth	1.5 years	2 years	group
Alb(g/L) ¹	26.2±1.47	27.0±0.9\$	28.2±0.8\$\$	29.1±1.0\$\$	30.0±1.2\$\$	30.5±1.1\$\$	A
	27.0±1.7*	28.7±0.9&,\$	29.9±1.0&,\$\$	31.2±0.9&,\$\$	34.0±1.9&,\$\$	32.6±2.1&,\$\$	B
ALT(U/L) ¹	28.8±24.7	28.7±24.3#	28.6±24.1#	28.9±23.7#	29.1±24.1#	28.4±23.8#	A
	24.1±10.2*	24.0±9.4*,\$	23.9±7.7*,\$	24.5±5.3*,\$	22.0±5.6*,\$	23.8±4.3*,\$	B
AST(U/L) ¹	45.0±24.2	45.6±25.1#	46.0±24.9#	47.2±26.1#	44.8±23.5#	45.7±23.6#	A
	35.9±11.6*	36.3±12.6*,\$	37.9±13.4*,\$	35.4±11.8*,\$	37.1±14.2*,\$	34.3±10.9*,\$	B
CHE(U/L) ¹	2817.2±1071.8	2908.4±996.9#	2964.8±955.0#	3071.2±902.1#	3066.4±863.1#	2955.1±618.9#	A
	2657.4±782.3*	2825.5±720.5*,\$	3198.3±534.8*,\$	3455.0±632.4*,\$	3477.9±551.2*,\$	3226.9±293.0*,\$	B
TC (mmol/L) ¹	2.70±0.83	2.67±0.53#	2.70±0.83#	2.80±0.40#	2.74±0.39#	2.72±0.47#	A
	2.37±0.23*	2.52±0.21*,\$	2.40±0.18*,\$	2.78±0.24*,@	2.83±0.29*,@	2.76±0.32*,\$	B
TBIL (μmol/L) ¹	31.9±26.2	42.9±25.2#	48.7±24.5@	51.2±15.3@	50.0±14.7@	50.2±7.9\$	A
	25.3±6.9*	23.9±4.8▲,#	26.0±4.7▲,#	25.7±2.7&,#	27.6±4.9&,#	27.5±2.5&,#	B
Cr (μmol/L) ¹	79.1±34.1	80.5±30.1#	79.7±33.1#	80.4±32.6#	79.2±28.9#	79.7±30.4#	A
	64.8±16.5	61.1±16.9*,\$	63.6±16.9*,\$	65.4±13.9*,\$	67.1±14.3*,\$	67.3±13.9*,\$	B
PT(s) ¹	20.2±2.8	20.8±2.1#	21.8±2.1\$	22.7±2.0\$	23.0±1.6\$	23.5±1.3\$	A
	21.6±2.5*	20.2±1.6*,\$	19.1±1.2Δ,\$	18.9±1.1&,\$	18.9±0.9&,\$	20.7±0.7&,\$	B
INR ¹	1.72±0.29	1.88±0.25\$	1.96±0.21\$	1.97±0.16\$	1.97±0.13\$	2.04±0.13\$	A
	1.71±0.19*	1.77±0.13*,\$	1.81±0.12*,\$	1.81±0.09Δ,#	1.86±0.12▲,#	1.89±0.09Δ,\$	B
HBVDNA (log copies/ml) ¹	8.5±8.2	3.24±3.09\$	Negative	Negative	Negative	Negative	A
	3.66±1.29*	2.98±1.13*,\$	Negative	Negative	Negative	Negative	B
HCV RNA	5.25±1.04	5.05±1.14#	5.20±1.21#	5.25±1.04#	5.15±1.17#	4.88±1.45#	A
	5.27±1.00*	5.19±1.21*,\$	4.89±1.57*,\$	5.1±1.34*,\$	4.92±1.29*,\$	4.99±1.38*,\$	B

¹ mean±SD; *p>0.05, ▲p<0.05, Δp<0.01, &p<0.001, compared to group A; #p>0.05, \$p<0.05, @p<0.01, \$\$p<0.001, compared to pre-treatment values.

Table 4 Clinical outcomes of cirrhotic patients treated with TIPS alone or simultaneous combined TIPS and PSE.

Outcome, n(%)	Group A (n=114)	Group B (n=27)	P values
Mortality			
Overall death	25(21.9%)	1(3.7%)	0.028
Cirrhosis-related death	23(20.5%)	1(3.7%)	0.038
Causes of death			
Variceal rebleeding	0	0	--
Sepsis	2(1.8%)	0	NS
Hepatic cancer	5(4.4%)	0	NS
Hepatic encephalopathy	5(4.4%)	0	NS
Hepatorenal syndrome	4(3.5%)	0	NS
Liver failure	9(7.9%)	1	NS
Hospital stays(days)*	14.2±2.0	13.9±1.6	NS

*Mean± SD.

DISCUSSION

Portal hypertension is the most common complication of chronic liver disease. It is responsible for the development of gastroesophageal varices, ascites, hepatorenal syndrome, bacterial infection, HE and hypersplenism, which are the main causes for the morbidity and mortality of liver cirrhosis^[20].

TIPS has been well documented in the treatment of esophagogastric variceal bleeding due to portal hypertension in cirrhosis^[3,21]. Consistent with these studies, variceal bleeding in our study decreased significantly in all patients receiving TIPS. Despite PSE being reported as efficacious in reducing variceal bleeding^[8] by reducing portal venous flow and pressure, combined therapy using TIPS and PSE in our study did not achieve significantly more reduced variceal bleeding compared to that of patients receiving TIPS alone, which might be related to the already very low bleeding frequencies obtained by creation of TIPS.

HE is a very common complication in patients after TIPS procedure. 20-31% of the patients who undergo a TIPS procedure would demonstrate new or worsening incidence of HE after TIPS^[1]. Consistent with this report, patients receiving TIPS alone in our study had significantly elevated frequencies of HE. Hiroshi Yoshida *et al*^[12] reported that PSE following obliteration of portal-systemic shunt reduces serum ammonia levels, and improves portal systemic encephalopathy, which might explain the result observed in our study that HE in group B did not worsen significantly, and was significantly lower than that of group A.

Previous studies^[6,19] demonstrated that WBC and PLT counts after PSE increased significantly than those before PSE. Consistent with these findings, patients receiving TIPS and PSE in our study had significantly increased WBC and PLT counts. Our study also showed increased levels of HGB in both groups, with patients receiving combined therapy of TIPS and PSE having higher HGB levels, which may be related to reduced blood loss obtained by TIPS and reduced intrasplenic destruction of RBC obtained by PSE. Bernd Saugel *et al*^[22] reported that the TIPS procedure led to a significant increase in serum bilirubin level, ALT and AST levels, and INR level as well. Earlier studies^[23,24] reported that TIPS can result in a deterioration of the liver function in the form of elevation of bilirubin, ALT and AST, probably due to reduction of hepatic blood flow and sinusoidal blood flow resulting from diversion of portal blood through a TIPS, which is even more obvious in patients with advanced liver disease due to incomplete hepatic artery buffer response^[25]. Compatible with these studies, our study showed that TBIL, PT, INR, and ALT and AST levels had significantly increased after TIPS in group A, but ALT and AST levels normalized by the 1st month posttreatment. Previous study^[11] demonstrated that PSE has beneficial effects on liver

function, enhancing hepatic protein synthesis capacity. The mechanism of improved liver function following PSE could be attributed to hemodynamic changes after PSE, which reduces portal venous flow, leading to a compensatory increase of blood flow in hepatic artery and superior mesenteric artery and vein^[26,27]. This hemodynamic change may result in more nutritious blood flow to the liver, and may improve liver function and induce liver regeneration in cirrhotics^[28,29]. Thus, we speculate that reduced HE may also be related to improved liver function following hemodynamic change brought on by PSE.

Regarding the effects of TIPS on survival, previous studies showed conflicting results. In two studies^[30,31], survival was found to be higher after TIPS, while two other studies failed to show any difference^[32,33]. Garcí'a-Pagán *et al*^[2] reported that early ePTFE-covered TIPS in highly selected patients with cirrhosis and acute variceal bleeding was associated with significant reductions in treatment failure and mortality. Our study demonstrated that combined therapy using TIPS and PSE was also associated with significant reductions in overall and cirrhosis-related mortality compared to TIPS alone, which may be attributed to reduced HE, improved liver function following combined PSE.

Michael Malinchoc *et al*^[34] reported that serum concentrations of bilirubin and Cr, INR, and the cause of the underlying liver disease were predictors of survival in patients undergoing elective TIPS, either for prevention of variceal rebleeding or for treatment of refractory ascites. In our study, Cox proportional-hazards regression showed that pretreatment MELD score, HE and group were independent predictors for cirrhosis-related mortality.

Our study was a retrospective study and had a few limitations. First, the number of patients in group B was relatively small. Second, the treatment assignment was not done by randomization, which seems impossible in real clinical practice, since TIPS is a very costly and complicated procedure and addition of PSE increases the cost and risk. Thus, there were some differences in the baseline characteristics of patients in two groups.

In conclusion, our study showed that simultaneous combined TIPS and PSE regimen improves hematologic parameters, prevents deterioration of liver function and coagulation function, reduces variceal bleeding and HE, thus reduces mortality.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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