THERAPEUTIC EFFICACY OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNT ON CIRRHOTIC PORTAL HYPERTENSION

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ABSTRACT

Backgroud: *This study aimed to explore the therapeutic efficacy of transjugular intrahepatic portosystemic stent shunt (TIPSS) on cirrhotic portal hypertension.*

Materials and methods: *A total of 117 patients with cirrhotic portal hypertension admitted to our hospital from February 2014 to February 2016 were enrolled for prospective analysis. Among them, 61 patients were treated with TIPSS as the research group, while the other 56 patients were treated with percutaneous transhepatic variceal embolization (PTVE) treatment as the control group. The clinical efficacy, incidence of adverse effects, liver function, and prognosis were compared between the two groups.*

Result: *There was no significant difference in the incidence of adverse effects and prognosis between the two groups (all $P>0.050$). The clinical treatment rate of the research group was significantly higher than that of the control group ($P<0.001$). And liver function and blood flow were significantly better than the control group ($P<0.001$).*

Discussion and conclusion: *TIPSS is more effective than PTVE in the treatment of patients with cirrhosis and portal hypertension, but it is necessary to pay close attention to the patient's blood pressure reduction to prevent hepatic encephalopathy.*

Keywords: *TIPSS, PTVE, cirrhosis, portal hypertension, upper gastrointestinal bleeding, MELD, Child-Pugh.*

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Introduction

Cirrhosis is a common clinical chronic disease, which causes liver injury from one or more reasons(1). According to statistics, the incidence of cirrhosis has reached 13.2/100,000 at present(2).

In recent years, more studies have shown that the incidence of cirrhosis is increasing year by year(3, 4). The common clinical cirrhosis mainly include post-hepatitis cirrhosis, alcoholic cirrhosis, parasitic cirrhosis, toxic cirrhosis, biliary cirrhosis, congestive cirrhosis and malnutrition cirrhosis(5). There is a large regional difference in the incidence of the disease. In Europe and the United States, alcoholic cirrhosis is the main disease, while viral cirrhosis is more common in large population countries such as China and India(6, 7). At present, the pathogenesis of cirrhosis has been widely recognized. It is considered that cirrhosis is mainly caused by progressive fibrosis in the liver(8). However, there are no obvious special clinical symptoms in the early stage of disease development, healthy liver tissues can still complete normal daily metabolic activities when mild lesions occur, so they are often easily ignored by patients(9). According to statistics, a large number of patients with cirrhosis have developed into advanced stage(10), which is one of the reasons for the high mortality of cirrhosis. The lethal threat of cirrhosis is usually not caused by the disease itself, but by the complications of cirrhosis(11).

The most common complication is massive hemorrhage in the upper digestive tract caused by portal hypertension, which is also one of the most lethal complications(12).

The results of Fujiyama et al.[13] showed that among 3685 patients with liver disease, 1264 patients suffered from portal vein tumor thrombus, while among the remaining 2421 patients with cirrhosis, 1666 patients were diagnosed as cirrhosis and portal hypertension.

In the face of the growing threat of cirrhosis to the human body, researchers are constantly striving to find new methods to effectively diagnose and treat cirrhosis. TIPSS is a new interventional radiotherapy for the treatment of portal hypertension and upper gastrointestinal hemorrhage[14].

Based on the principle of shunt, TIPSS establishes an manual shunt channel between hepatic vein and portal vein in hepatic parenchyma to reduce the pressure of portal vein blood flow and the rupture of blood vessels and massive hemorrhage caused by portal hypertension[15]. At present, TIPSS has gradually been widely used in clinic, but there are still some controversies due to its indications and complications of hepatic encephalopathy[16]. Therefore, this experiment analyzed the application value of TIPSS and PTVE, and explored the application value of TIPSS in a comprehensive way, providing reference and guidance for clinical.

Materials and methods

General information

A total of 117 patients with cirrhotic portal hypertension admitted to our hospital from February 2014 to February 2016 were enrolled for prospective analysis, including 71 males and 46 females between 45 and 72 years, with an average age of (59.8±8.6) years. Among them, 61 patients received TIPSS treatment as the research group, and 56 patients received PTVE treatment as the control group.

Inclusion of exclusion criteria

Inclusion criteria were as follows:

- Compliance with the clinical diagnostic guidelines for cirrhosis[17];
- Diagnosis of cirrhosis after a series of examinations in our hospital;
- Combination of portal hypertension and gastrointestinal bleeding;
- 20 to 75 years old;
- Surgical treatment in our hospital;
- An informed consent signed by the patient himself or his immediate relatives.

Exclusion criteria were as follows:

- Patients with tumors; patients with other cardiovascular and cerebrovascular diseases;
- Patients with other infectious diseases or autoimmune diseases;
- Patients with other severe organ dysfunction; severe portal vein thrombosis (portal occlusion >50%) or cavernous transformation;
- Patients with cerebral encephalopathy;
- Patients transferred to our hospital;
- Patients with surgical contraindications;
- Long-term bedridden patients with physical disability.

Methods

The operation of both groups was performed by senior clinicians in our hospital. PTVE operation plan of the control group: preoperative ultrasound localization was performed to determine the needle insertion site, needle insertion point, needle insertion path, and target vessel distance according to the dilated intrahepatic vein.

The 22G Chiba needle was used to puncture the target vessel under the guidance of the X-ray, and the needle core was withdrawn slowly. The guide wire was inserted through the external cannula, and the pig tail catheter was replaced by splenic venography. The portal vein system was confirmed to be free of stenosis. Simena was replaced with gastric coronal vein after embolization, and the contrast agent was injected to embolize.

Venography was satisfactory for the posterior tube. The TIPSS surgical plan of the research group: The venous access was established in the right neck, the portal vein was punctured through the jugular vein, and the spleen-portal venography was performed after the puncture.

After the portal vein pressure was achieved, the esophageal and gastric varices were evaluated and embolized. After balloon dilatation, the stent was inserted to measure the portal vein pressure again, and the portal vein pressure was controlled below 12 mmHg.

Observation indicators

Clinical efficacy

There was no bleeding within 1 to 2 days after operation, clinical symptoms and related signs disappeared without complications (including splenomegaly, hyperhepatia, ascites, and portal collateral circulation), no disease recurrence within 30 days was judged to be markedly effective; bleeding was well controlled within 1 to 2 days after operation, clinical symptoms were improved and no complications were judged to be effective; no significant improvement of all postoperative symptoms was judged as ineffective[18]. The clinical treatment rate of the two groups of patients = (markedly effective + effective) / total *100%.

Negative effects

Adverse reactions and complications were recorded and the incidence of negative effects was calculated.

Liver function

total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), serum creatinine (SCr). The test was performed 3 days before surgery and 3 days after surgery. MELD score[19] and Child-Pugh score[20].

Prognostic Survival

The patients were followed up for two months, and the prognosis of the two groups was recorded in the form of hospital review. Hemodynamics: portal vein pressure, portal vein diameter and blood flow velocity were measured 3 days before operation and 3 days after operation, respectively.

Statistical methods

All the experimental results were statistically analyzed using SPSS24.0 (Beijing Sichuang Weida Information Technology Co., Ltd.) and figures were drawn using GraphPad Prism 8 (Shenzhen Tianruiqi Network Co., Ltd.). Measurement data such as patient age and portal vein pressure were expressed as the mean ± standard deviation, and t-test was used for comparison between groups.

Counting data such as clinical efficacy and negative effects were expressed as percent (%). A chi-square test was test was used for comparison between several groups. The survival rate was calculated by Kaplan-Meier method, and the survival rate was compared by Log-rank test. P<0.050 was considered statistically significant.

Results

General data comparison

The age, BMI, diastolic blood pressure, systolic blood pressure, red blood cells, white blood cells, platelets, gender, living environment, smoking, drinking status, education level and etiology were not significantly different between the two groups (all P>0.050). See Table 1.

	Research group (n=61)	Control group (n=56)	t or χ^2	*p*
Age			0.952	0.343
	59.2±8.8	60.7±8.2		
BMI (KG/cm^2)			0.463	0.737
	25.62±3.16	25.18±3.30		
Diastolic blood pressure (mmHg)			0.692	0.490
	118.67±8.84	119.82±9.12		
Systolic blood pressure (mmHg)			0.647	0.459
	168.21±7.26	168.86±8.05		
Red blood cell (×10^{12}/L)			0.121	1.562
	5.99±0.42	6.12±0.48		
Leukocyte (×10^9/L)			0.348	0.943
	7.62±1.06	7.81±1.12		
Platelet (×10^9/L)			0.183	1.339
	219.62±34.86	227.81±30.96		
Gender			0.149	0.700
Male	36 (59.02)	35 (62.50)		
Female	25 (40.98)	21 (37.50)		
Living Environment			0.426	0.514
Town	52 (85.25)	50 (89.29)		
Rural	9 (14.75)	6 (10.71)		
Smoking			0.484	0.487
Yes	47 (77.05)	40 (71.43)		
no	14 (22.95)	16(28.57)		
Drinking			0.042	0.837
Yes	36 (59.02)	32 (57.14)		
No	25 (40.98)	24 (42.86)		
Educational level			0.243	0.622
<high school	41 (67.21)	40 (71.43)		
≥high school	20 (32.79)	16 (28.57)		
Cause of disease			0.867	0.990
Alcoholic hepatitis	14 (22.95)	11 (19.64)		
Viral hepatitis	10 (16.39)	10 (17.86)		
Autoimmune hepatitis	12 (19.67)	9 (16.07)		
Hepatitis B	8 (13.11)	8 (14.29)		
Hepatitis C	6 (9.84)	5 (8.93)		
Simple cirrhosis	9 (14.75)	11 (8.93)		
Other	2 (3.28)	2 (3.57)		

Table 1: Comparison of general data between the two groups of patients [n (%)].

Comparison of clinical efficacy

The research group showed a treatment rate of 91.80%, with 36 markedly effective patients (59.02%), 20 effective patients (32.79%), and 5 ineffective patients accounted for (8.20%), and the control group showed a treatment rate of 78.57%, with 20 markedly effective patients (35.71%), 24 effective patients (42.86%), and 12 ineffective patients (21.43%). The treatment rate in the research group was significantly higher than that in the control group (P=0.043). See Table 2.

	Research group (n=61)	Control group (n=56)	χ^2	*p*
Markedly effective				
	36 (59.02)	20 (35.71)		
Effective				
	20 (32.79)	24 (42.86)		
Ineffective				
	5 (8.20)	12 (21.43)		
Treatment rate (%)			4.116	0.043
	91.80	78.57		

Table 2: Comparison of clinical efficacy between the two groups of patients [n (%)].

Comparison of negative effects

The incidence of negative effects was 13.11% in the research group and 14.29% in the control group. There was no significant difference between the two groups (both P>0.050). See Table 3.

	Research group (n=61)	Control group (n=56)	χ^2	*p*
Gastrointestinal bleeding				
	1 (1.64)	3 (5.36)		
Balloon expansion				
	0 (0.00)	1 (1.79)		
Incision infection				
	1 (1.64)	1 (1.79)		
Hepatic encephalopathy				
	6 (9.84)	2 (3.57)		
Thrombus				
	0 (0.00)	1 (1.79)		
Negative impact rate (%)			0.033	0.854
	13.11	14.29		

Table 3: Comparison of negative effects between the two groups of patients [n (%)].

Comparison of liver function

There was no significant difference in TP and SCr between the two groups before and after operation (both P>0.050), and no significant difference in TBIL, AST and ALT before and after operation (all P>0.050).

The levels of TBIL, AST and ALT in the research group were significantly lower than those in the control group (all P<0.001). The levels of TBIL, AST and ALT after operation in both groups were significantly higher than those before operation (all P<0.001). See Figure 1.

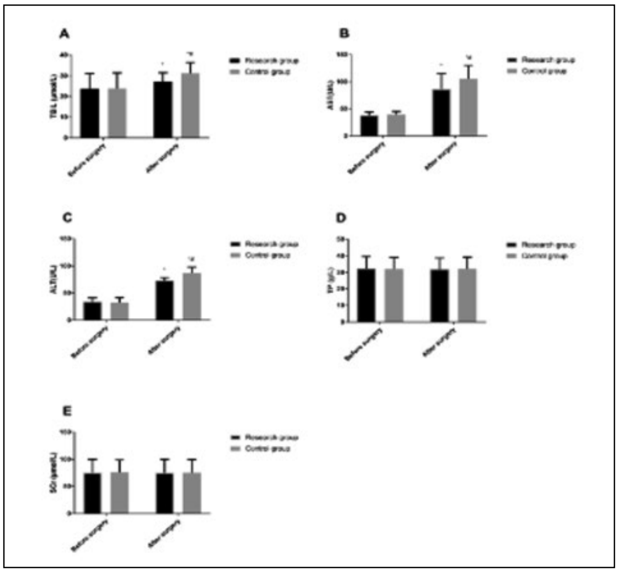

Figure 1: Comparison of liver function between two groups before and after operation.

*A) Comparison of TBIL before and after surgery in both groups; B) comparison of AST before and after surgery in two groups; C) comparison of ALT before and after surgery in two groups; D) comparison of TP before and after surgery in two groups; E) comparison of SCr before and after surgery in two groups. *indicates compared with the same group before surgery, P<0.001; #indicates compared with the research group after surgery, P<0.001.*

Comparison of MELD and Child-Pugh score

The MELD score of the research group was 15.21±2.18 after surgery, significantly higher than that of the control group (P<0.001). The Child-Pugh score was 12.85±2.86, significantly lower than the Child-Pugh score after surgery. See Figure 2.

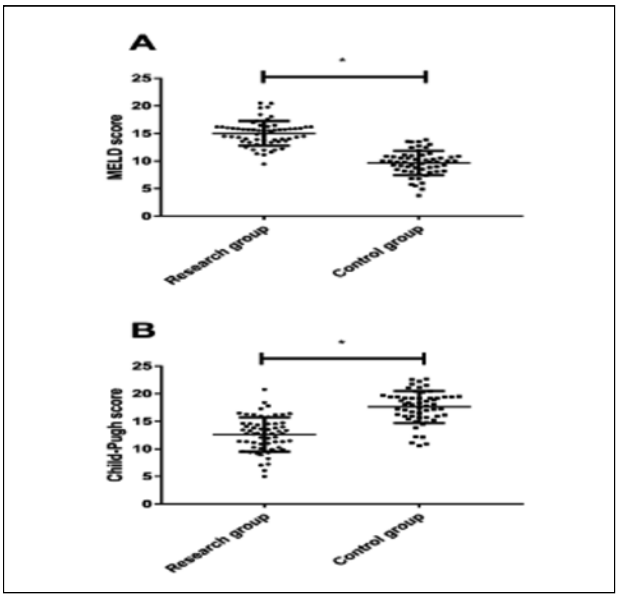

Figure 2: Comparison of MELD and Child-Pugh score between the two groups.

*A) MELD score was compared between the two groups, *P<0.001; B) Child-Pugh scores was compared between the two groups, *P<0.001.*

Comparison of prognosis

Patients in the two groups were followed up for a period of 2 months, and 116 patients were successfully followed up, with a success rate of 99.15%. One case was lost to follow-up in the research group. There was no significant difference in the prognosis between the two groups (P>0.050). See Figure 3.

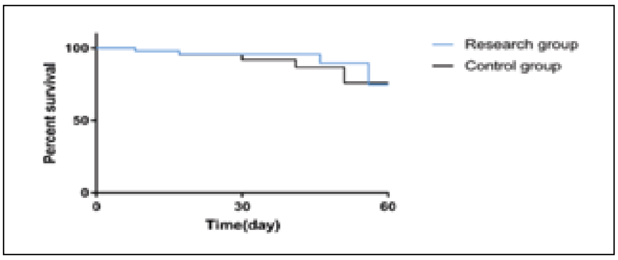

Figure 3: 2-month percent survival curve of prognosis in two groups.

Comparison of hemodynamic

There was no significant difference in portal vein pressure, diameter of portal vein and blood flow velocity between the two groups before operation (all P>0.050). After operation, the pressure, diameter and velocity of portal vein in the research group were significantly lower than those in the control group (all P<0.001). See Figure 4.

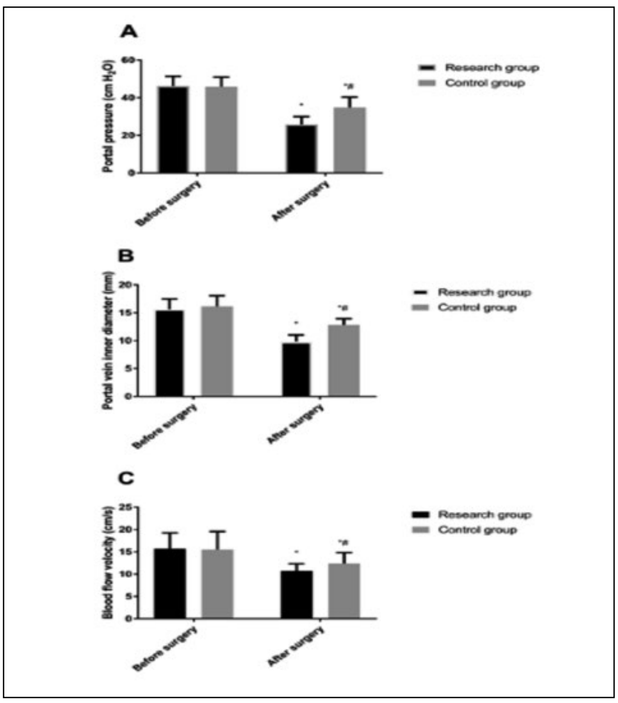

Figure 3: Comparison of Hemodynamic between two groups before and after operation.

*A) Comparison of portal pressure before and after operation in two groups; B) comparison of portal vein inner diameter before and after operation in two groups; C) comparison of blood flow velocity before and after surgery in two groups. *indicates compared with the same group before surgery, P<0.001; #indicates compared with the research group after surgery, P<0.001.*

Discussion

Portal hypertension in cirrhosis is the main cause of upper gastrointestinal bleeding and one of the main causes of poor prognosis in patients. In order to effectively interfere with cirrhosis portal hypertension, we have been working to explore an effective treatment(21-23). PTVE is one of the most common treatment methods at present. It can prevent and cure variceal bleeding by percutaneous puncture of intrahepatic portal vein branches under the guidance of ultrasound(24).

Its application value has been confirmed, but with the development of the patient's condition, the shortcomings of PTVE are gradually exposed. Therefore, the use of TIPSS has gradually received clinical attention. TIPSS can reduce portal hypertension by establishing a restrictive shunt channel in portal vein and hepatic vein, which has higher safety(25). This study aims to explore the application value of the two treatment methods in patients with cirrhotic portal hypertension.

The results of this experiment showed that the clinical efficacy of the patients treated with TIPSS was significantly better than that of the control group treated with PTVE, but there was no significant difference in the incidence of adverse effects between the two groups, suggesting that TIPSS is more suitable for the treatment of patients with cirrhotic portal hypertension.

During the treatment of PTVE, embolic agents need to be injected into the communicating branches of the right gastric artery and the gastric fundus vein. In the process of blood circulation, embolic agents flow to the peripheral circulation, blocking the blood flow of the lower esophagus, the gastric fundus and the extramural vessels of the stomach, as well as the internal and external reflux of the gastroesophageal wall, thus blocking the bleeding of the gastric fundus(26).

In the early stage of development, TIPSS patients have a high probability of restenosis due to the use of bare stents(27). With the development of medical technology, polytetrafluoroethylene (PTFE) peritoneal stent is currently used in TIPSS, which has high shunt patency rate and low straightening rate(28). However, the different levels of negative reactions in both groups may be caused by inflammatory in the body due to bile leakage.

The incidence of patients with hepatic encephalopathy in the research group reached 9.84%, which was the most common postoperative complication of TIPSS[29]. The mechanism is mainly due to the direct influx of portal vein blood into the systemic circulation without liver metabolism and the decrease of liver metabolic capacity[30].It may also be due to the fact that there are too few cases in this studyand the result is accidental. At present, there is no research to confirm which interventions can reduce the incidence of hepatic encephalopathy during TIPSS.

We suspect that small diameter stents may have some intervention effect, but due to the lack of experimental support, we hope that in the future it can be used as a research direction for domestic and foreign scholars to carry out more in-depth research. Comparing the liver function of the two groups, we found that there was no significant difference in TP and SCr between the two groups, but the liver function of the research group was significantly better than that of the control group, which also indicated that TIPSS had less damage to the liver function of the patients.

The reason may be that the liver blood supply is mainly from the portal vein and a small part is from the hepatic artery[31]. However, both of the two treatments affect portal venous perfusion in varying degrees, so the liver failed to compensate in time resulted in TBIL, AST and ALT elevation. It may also due to the fact that AST and ALT increased the permeability of the cells when the corresponding cells were damaged, and they were released into the blood in large quantities, increasing their levels, which may be related to the stress injury caused by puncture.

MELD score is one of the most commonly used indicators to judge the short-term prognosis of patients with liver diseases. The results in this paper showed that the MELD score of the research group was significantly higher than that of the control group after treatment. Reverter et al.[32] showed that the prognosis of patients with higher MELD was generally better, but PENG et al.[33] indicated that the evaluation of liver disease by MELD had different performance for different populations, which could also be used as a further direction for further analysis and discussion in this study.

The Child-Pug score showed that the research group was significantly lower than the control group, which also indicated that the research group patients may have a better prognosis. Therefore, we followed up the prognosis of the two groups for two months, and found that there was no significant difference in survival between the two groups.

This may be due to the small sample size and short follow-up time of this study, which requires a longer follow-up survey. Further comparison of the blood flow between the two groups of patients revealed that blood flow dynamics changed in both groups after treatment, and TIPSS could directly divert portal blood flow to the systemic circulation, reducing portal pressure gradient.

However, insufficient portal vein pressure after operation is prone to re-bleeding, and excessive reduction of portal pressure is likely to induce hepatic encephalopathy[34].

This is also consistent with the results of this experiment, suggesting that in the future clinical practice of TIPSS for patients with cirrhosis, it is necessary to pay close attention to the antihypertensive of the patient's portal vein to prevent the occurrence of hepatic encephalopathy.

In conclusion, TIPSS is more effective than PTVE in the treatment of patients with cirrhosis and portal hypertension, but we need to pay close attention to the antihypertensive of the patient's portal vein to prevent the occurrence of hepatic encephalopathy.

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Availability of data and materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions:
ZL wrote the manuscript. LL interpreted and analyzed the patient data. JLL and LC designed the study and performed the experiment. JYL and JH were responsible for the analysis and discussion of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate:
The study was approved by the Ethics Committee of The 980 Hospital of PLA Logistic Force. Patients who participated in this research, signed the informed consent and had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

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