Cover Page

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Contents

Original protocol

Transjugular intrahepatic portosystemic shunt for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: Study protocol for a randomized controlled trial

Background

Variceal bleeding is a common and serious complication of advanced liver cirrhosis [1-3]. The incidence of a first variceal bleeding within one year is about 12% in cirrhotic patients with gastro-esophageal varices [2-3]. The incidence of variceal rebleeding within one year is 60% in cirrhotic patients with a previous history of variceal bleeding, and the mortality from each rebleeding episode is nearly 20% [2-4]. The presence of portal vein thrombosis (PVT) further increases the incidence of variceal rebleeding in cirrhotic patients [5].

The current therapeutic algorithm for the secondary prophylaxis of variceal bleeding in liver cirrhosis includes non-selective beta-blockers (NSBBs) combined with endoscopic therapy (ET) as the first-line choice of therapy and TIPS as the second-line therapy [2-3, 6]. This recommendation is mainly because the rate of hepatic encephalopathy is significantly higher in patients undergoing TIPS than in those receiving NSBBs and ET, but the overall survival is not improved [7-9]. However, the therapeutic algorithm could not be readily extrapolated to cirrhotic patients with PVT.

On the other hand, the efficacies of anticoagulation therapy and transjugular intrahepatic portosystemic shunt (TIPS) for recanalizing PVT in liver cirrhosis have been shown in several case series [10-13]. However, the limitations of the two treatment modalities are clear. First, anticoagulation therapy appears to be effective for recanalizing partial PVT rather than complete PVT or cavernous transformation of the portal vein [14-15]. Second, if anticoagulation therapy was used in cirrhotic patients with a history of variceal bleeding, the risk or severity of bleeding might be further exacerbated [16-17]. Third, the TIPS technique in the presence of PVT is relatively difficult [18], and the procedure-related complications are potentially lethal [18-19]. Due to the absence of randomized controlled studies, no definite treatment algorithm for the management of variceal rebleeding in liver cirrhosis and PVT has been well established in the Baveno V consensus and recent American Association for the Study of Liver Diseases (AASLD) practice guidelines on the management of vascular disorders of the liver [20-21].

We hypothesize that TIPS may be superior to conventional therapy for the prevention of variceal rebleeding in liver cirrhosis patients with non-tumoral PVT [22]. Thus, a randomized controlled trial (RCT) is being conducted at our center to explore this issue.

Methods/Design

Study Design

This is a randomized controlled study evaluating TIPS versus conventional therapy (i.e., ET combined with NSBBs) for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT who had bled within the past 6 week (**Figure 1**).

Cirrhotic patients with PVT presenting with an acute upper gastrointestinal bleed underwent emergency upper gastrointestinal endoscopy. Acute esophageal variceal bleed was diagnosed if active bleeding was seen from the varix, a white nipple or a clot was seen on the varix, or if there was blood in the stomach in a patient with an esophageal varix and no other potential bleeding source. If esophageal varices were found to be the cause of bleed, these patients underwent band ligation and also were given vasoactive drugs (terlipressin or somatostatin) for 5 days. Those patients who had a failure of primary hemostasis during acute bleed were excluded from the study. On day 6 of acute bleed, patients were screened and if found to satisfy the inclusion and exclusion criteria, were enrolled and randomly assigned to receive either endoscopic variceal ligation (EVL) +propranolol or TIPS for secondary prophylaxis. Thus, day 6 of acute bleed formed day 1 of randomization in patients presenting with acute bleed.

Those patients with PVT who presented with a history of recent bleed from esophageal varices and satisfying the inclusion and exclusion criteria were enrolled and randomized on day 1 to receive either TIPS or EVL + propranolol. Patients who previously had received more than one session of ligation/sclerotherapy were excluded.

All subjects who meet the entry criteria will be randomized at a ratio of 1:1 to receive either TIPS or conventional therapy. This study is being performed in the Departments of Liver Disease, Digestive Interventional Radiology, Endoscopy, and Ultrasound of Xijing Hospital of Digestive Diseases, Fourth Military Medical University.

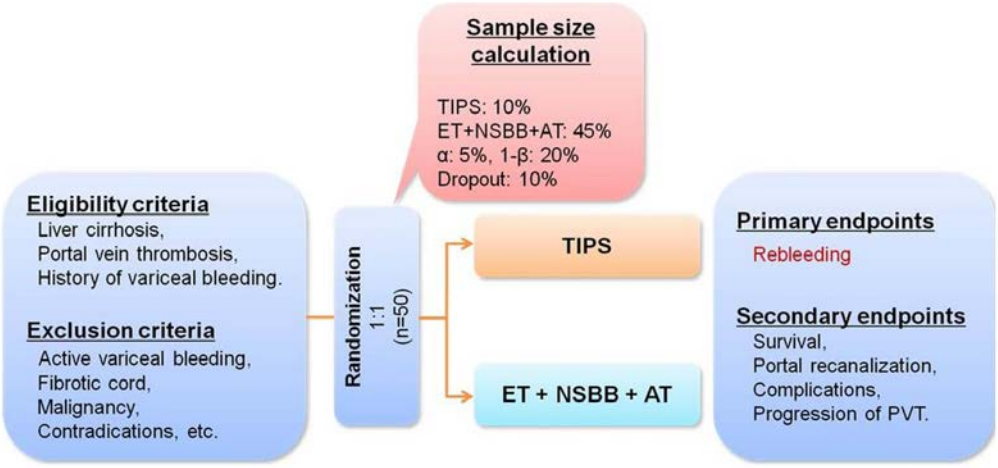

Figure 1 Study design.
Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic therapy; NSSB, non-selective beta blocker; AT, anticoagulation; PVT, portal vein thrombosis.

Inclusion criteria

- Written informed consent.
- Adult patients (aged 18-75 years old).
- Diagnosis of liver cirrhosis (liver cirrhosis is diagnosed by clinical presentations, laboratory tests, images, and liver biopsies).
- Diagnosis of PVT (axial computed tomography [CT] scans demonstrate that thrombus occupies >50% of the portal vein lumen with or without portal cavernoma).
- History of variceal bleeding within past 6-weeks (all subjects will undergo endoscopy to confirm that the upper gastrointestinal bleeding originates from the esophageal and gastric varices rather than other potential sources).

Exclusion criteria

- Uncontrolled active variceal bleeding (the time frame of the acute bleeding episode should be 120 hours [18]).
- Thrombus occupies <50% of the portal vein lumen.
- The thrombosed portal trunk is progressed to the fibrotic cord (the patients will be included, if the interventional radiologists consider that the diameter of a collateral vessel is large enough to place a stent [8, 17]).
- History of TIPS placement or shunt surgery (the patients will be included, if the surgical shunt is completely occluded or invalid).
- Concomitant renal insufficiency.
- Severe cardiopulmonary diseases.
- Uncontrolled systemic infection or sepsis.
- Malignancy or other serious medical illness that may reduce life expectancy.
- Contraindications for propranolol.
- Contraindications for heparin or warfarin.
- Contraindications for TIPS.
- Pregnant or breast-feeding subjects (before enrollment, human chorionic gonadotropin is measured in all female patients).
- Subjects unable to swallow oral medications.

Informed consent

All relevant information regarding the clinical trial is included in informed consent forms in the Chinese language. Further, the investigators (HC, HG, YZ, and QX) will provide a detailed explanation of this trial to the eligible patients. Informed consent must be signed by all patients or their relatives if the informed consent cannot be signed by the patients themselves. All patients' personal data and medical information will be kept confidential. All patients will be permitted to withdraw from this trial at any time.

Randomization

After the eligible patients give informed written consent, they will be stratified according to the Child-Pugh class (Child-Pugh class A= 5-6 points, Child-Pugh class B= 7-9 points, Child-Pugh class C= 10-15 points) [23] and the degree of PVT (partial obstruction, complete obstruction, obliterative portal vein) [8, 24]. The patients will then be randomized into the TIPS and Conventional Therapy groups by means of a web-based randomization system (http://openrct.fmmu.edu.cn). This system has been established by two investigators (CH and XJ) from the Department of Statistics of the Fourth Military Medical University.

Intervention

TIPS group

Patients assigned to the TIPS group will undergo TIPS insertions within 48 hours of randomization. All procedures will be performed with patients under conscious sedation and local anaesthesia by the same experienced interventional team (GH, CH, ZY, and WG) in which an experienced interventional radiologist and hepatologist (GH) is the operator with one of the others serving as first assistant, and a fellow as second assistant. Generally, both contrast-enhanced computed tomography and indirect portography via the superior mesenteric artery are initially employed to evaluate the portal venous system in all patients. If the intrahepatic portal vein branches could be visualised, a conventional transjugular approach will be the first choice. When indirect portography revealed poor or no visualisation of the portal vein and its branches, an ultrasound-guided percutaneous transhepatic approach will be employed to facilitate the TIPS procedure. When access of the intrahepatic portal vein branch was not feasible or failed, an ultrasound-guided percutaneous transsplenic approach will be attempted [8, 17, 25].

Transjugular approach Under the fluoroscopic guidance, an 18-gauge RUPS-100 needle (Rosh-Uchida TIPS set, Cook, Bloomington, USA) will be introduced into the hepatic vein through a long 5-F vascular sheath inserted into the internal jugular vein and punctured through the liver parenchyma from the hepatic vein to the portal vein. When the portal vein is accessed, a hydrophilic guidewire (Terumo, Tokyo, Japan) is used to navigate thrombosed/stenotic segments of portal vein eventually accessing the patent portion of the portal or splenic vein. Next, a portal venogram was performed and the portosystemic pressure gradient (PSG) will be measured. If large varices were identified, coil embolization of oesophagogastric varices was performed. The identified occluded portal vein and the intrahepatic tract is dilated using 8-10 mm/40 mm balloons (PowerFlex, Cordis, Tipperary, Ireland). A ePTFE covered stent (Fluency®, Bard, Tempe, AZ, USA) with a diameter of 8 mm and a length of 6-10 cm will be placed with their proximal end at the hepatocaval junction and their distal end in a patent portion of the portal venous system.If the first stent does not maintain sufficient intra-stent flow, an additional stent will be deployed coaxially. If a large collateral vein was present in patients in whom portal vein recanalisation is not feasible, TIPS placement will be considered to drain blood flow from the large collateral vein to the hepatic vein. The stents will be initially dilated to maximum obtain a good gradient.Finally, the PSG will

be remeasured and repeat portography was performed. If residual thrombus remains in the distal end of the stent, an indwelling venous catheter will be placed in the confluence of the superior mesenteric vein and splenic vein for local thrombolysis with bolus infusions of urokinase (500,000 units twice a day) for 3 days. If the occluded main portal vein or superior mesenteric vein cannot be recanalized or TIPS insertion fails, the patients will be treated with conventional therapy. A Doppler ultrasound was carried out within 2-7 days to evaluate shunt patency.

A combined transjugular/transhepatic or transjugular/transsplenic approach Under ultrasound guidance, the intrahepatic portal vein branch or a suitable splenic vein near the splenic hilum will be punctured with an 18-G PTC needle by the same well-trained doctor (WJ). Then, a 0.035-inch hydrophilic guidewire (Terumo, Tokyo, Japan) will be advanced and a 5-Fr introducer sheath (Terumo,Tokyo, Japan) was placed. The guidewire and a 5-Fr Cobra catheter (Cordis, Florida, USA) will be employed to probe the occlusion and to traverse the occluded portal vein into the superior mesenteric or splenic vein**.** Once the occlusion is traversed, the catheter will be retracted back with its tip positioned at the site of desired portal vein access and the guidewire left in the SMV or SV. Under fluoroscopic guidance, the transjugular Rosch-Uchida needle will be used to puncture the tip of catheter which served as a target. After confirming the desired portal vein successful puncture, a transjugular guidewire will advance through the needle into the portal system. Then a classical TIPS procedure will be performed to reconstruct hepatopetal blood flow.Both the transhepatic and transsplenic tracts will be embolized with coils after TIPS.

After the TIPS insertions, intravenous infusions of heparin (8,000-12,000 u/d) for five days followed by oral warfarin for 6 months will be routinely prescribed at doses that achieve an international normalized ratio (INR) of up to two times the upper limit of normal for the prevention of shunt dysfunction. Intravenous antibiotics for 4-5 days will be prescribed for the prevention of operation-related infections. If any evidence of shunt dysfunction is observed, TIPS revision by balloon angioplasty and additional stent-placement will be planned. If the shunt dysfunction cannot be revised, the patients will be treated with conventional therapy.

Shunt dysfunction will be suspected in any one of the following conditions: (1) recurrent variceal bleeding; (2) recurrent or gradually worsening ascites; or (3) the maximum flow velocity within the shunt is less than 50 cm/s or the flow velocity within the shunt is absent on color Doppler ultrasound (CDUS). Suspected dysfunction will be further confirmed, if shunt stenosis is greater than 50% on portography and/or the PSG is beyond 12 mmHg[8].

Conventional Therapy group

ET. Patients assigned to the Conventional Therapy group will undergo endoscopic variceal ligation (EVL) within 48 hours of randomization. According to the AASLD practice guidelines for the management of variceal bleeding [3, 26], varices are ligated every 1-2 weeks until they are obliterated or are considered inappropriate for ligation by endoscopists. Endoscopic screening for recurrent varices is arranged within 1-3 months after variceal obliteration, and a

repeat endoscopy is then conducted every 6 months. Recurrence of varices was defined as appearance or an increase in the grade of varices after achieving successful eradication or reduction in size of varices. If varices reappeared, further EVL sessions were initiated.

NSSBs. Patients assigned to the Conventional Therapy group will receive NSSBs immediately after randomization. According to the AASLD practice guidelines for the management of variceal bleeding [3, 26], propranolol should be started at a dose of 20 mg twice a day, and is adjusted to the maximum tolerated dose (160 mg twice a day) or until the heart rate is reduced to 55 b.p.m or 25% from baseline.

Anticoagulation. Patients assigned to the Conventional Therapy group will receive anticoagulants within 2 weeks after variceal obliteration. According to the American College of Chest Physicians (ACCP) guidelines for the management of deep vein thrombosis [27], intravenous infusions of heparin are initially administered at a dose of 1,000 units per hour for 5 days. Subsequently, oral warfarin should be started at a dose of 2.5 mg once a day, and is adjusted to achieve an INR of up to two times the upper limit of normal. Oral warfarin therapy will continue for 6 months or until portal vein complete recanalization.

NSBBs-induced adverse events include lightheadedness, fatigue, and shortness of breath, while the anticoagulant-induced adverse events include bleeding, thrombocytopenia with or without thrombosis, osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, and hypoaldosteronism. If adverse events are considered mild or moderate, the treatment will be continued or the dose of these drugs will be reduced until they disappear. If adverse events are considered severe or the patients are unable to tolerate these drugs, the treatment will be discontinued.

TIPS rescue**.** Patients assigned to the Conventional Therapy group will receive TIPS as a rescue therapy in any one of the following conditions: (1) one episode of clinically significant variceal re-bleeding after endoscopic therapy resulting in the development of hypovolemic shock or a 3 g drop in hemoglobin within any 24 h period if no transfusion is administered [18]; (2) two episodes of clinically significant re-bleeding (i.e., melena or hematemesis); or (3) one episode of clinically significant re-bleeding with pampiniform or racemose varices on endoscopy that are considered inappropriate for ligation or sclerotherapy by endoscopists.

Objectives

Primary objective

To compare the rate of variceal rebleeding between the patients undergoing TIPS and those receiving endoscopic therapy combined with NSSBs and anticoagulants.

Secondary objectives

- To compare the rate of overall death and variceal bleeding-related death between the two groups.
- To compare the rate of portal vein recanalization between the two groups.

- To compare the rate of complications between the two groups.
- To observe the progression of PVT in patients without portal vein recanalization.

Data collection

Paper case report forms have been designed for data collection by one investigator.

Upon enrollment, the following data will be collected:

- Demographic characteristics (sex and age).
- Physical examination parameters (blood pressure, heart rate, height, weight, shifting dullness, hepatomegaly, and splenomegaly).
- Disease history (the date of diagnosis of liver cirrhosis and PVT, the therapeutic methods of variceal bleeding, viral hepatitis, thrombosis at other sites, alcohol abuse, drug use, abdominal trauma and surgery, hematological disease, the use of oral contraceptives, and other diseases).
- Laboratory tests (red blood cells, hemoglobin, white blood cells, platelets, total bilirubin, direct and indirect bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glutamine transferase, urea nitrogen, serum creatinine, potassium, sodium, alpha-fetoprotein, prothrombin time, INR, and D-dimer).
- Electrocardiogram.
- Anteroposterior chest radiographs.
- Abdominal CDUS (liver, spleen, grade of ascites [28], and the extension and degree of PVT [24]).
- Abdominal CT scans (liver, spleen, grade of ascites, and the extension and degree of PVT).
- Upper gastrointestinal endoscopy (the location, form, and diameter of the varices and red color signs).
- Child-Pugh [23] and Model for End-stage Liver Disease (MELD) scores [29].

As the patients are allocated into the TIPS group, the following data will be collected:

- The overall duration of the TIPS procedure.
- Approaches used for the percutaneous puncture of the portal vein (transjugular, trans-hepatic, and trans-splenic approaches).
- Whether coil embolization of varices is performed.
- The number of coils if embolization is performed.
- The number of TIPS stents.
- Whether local thrombolysis is performed after stent placement.
- The PSG before and after TIPS.
- TIPS procedure-related complications (i.e., hepatic capsule perforation, stent displacement).
- Whether TIPS revision is performed.
- The number, duration, and methods (additional stent-placement and/or balloon angioplasty) of TIPS revision(s) if TIPS revision is performed.

As the patients are allocated into the Conventional Therapy group, the following data will

be collected:

- The overall duration of endoscopic therapy.
- The number of sessions required to eradicate the varices.
- The methods of endoscopic therapy (i.e., variceal ligation, and cyanoacrylate glue injection).
- The number of bands and volume of glue.
- Endoscopic therapy-related complications.
- The dose of propranolol used for adequate beta blockade.
- Heart rate at the time of adequate beta blockade.
- Whether propranolol is discontinued.
- The dose of warfarin used as the target INR is achieved.
- Whether warfarin is discontinued.
- Adverse events of propranolol and warfarin.

A regular follow-up flow chart will be established (**Figure 2**). The grade of varices will be evaluated by endoscopy. The Child-Pugh and MELD scores will be calculated. The extension and degree of PVT will be evaluated by abdominal CDUS and CT scans. According to previous studies [7, 30-31], portal vein recanalization is considered complete if the portal vein trunk, superior mesenteric vein, and splenic vein are patent; portal vein recanalization is considered partial if the degree of thrombosis within the portal vein trunk is decreased. Additionally, all enrolled patients will have telephone follow up with one investigator (WZ) regarding their conditions and drug use every week in the first month and once per month thereafter.

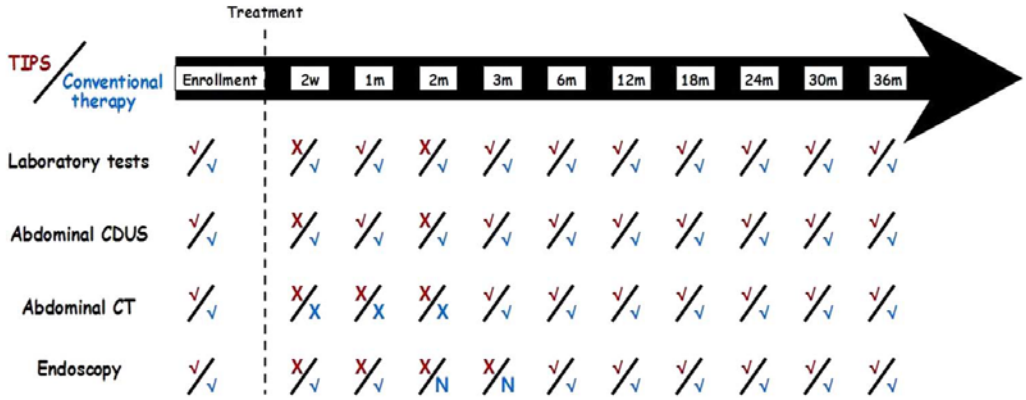

Figure 2 Regular follow-up flow chart.
Notes: √, performed; X, not performed; N, performed if necessary.
Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; CT, computed tomography; CDUS, color Doppler ultrasound.

As hepatic encephalopathy occurs, the following data will be collected:

- The number of episodes of hepatic encephalopathy.
- The starting time and duration of every episode of hepatic encephalopathy.
- The grade of every episode of hepatic encephalopathy according to the West Haven

Criteria [32].

- The treatment and outcome of every episode of hepatic encephalopathy.

As shunt dysfunction occurs, the following data will be collected:

- The number of episodes of shunt dysfunction.
- The starting time and duration of every episode of shunt dysfunction.
- The diagnosis, treatment, and outcome of every episode of shunt dysfunction.

As variceal bleeding recurs, the following data will be collected:

- The number of variceal rebleeds.
- The starting time and duration of every episode of variceal rebleeding.
- The causes of every episode of variceal rebleeding.
- The treatment and outcome of every episode of variceal rebleeding.

As any patient dies, the following data will be collected:

- The time of death after enrollment.
- The cause of death.

Reporting of adverse events

- ***An adverse event (AE)*** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- ***Serious adverse event (SAE)*** must be reported to the regulatory authorities immediately (within 24h), whereas **non-serious adverse events** are merely documented in the annual summary sent to the regulatory authority.
- ***Serious adverse event*** is defined as any untoward medical occurrence when the patient outcome is:
- ***Death*** Report if you suspect that the death will be an outcome of the adverse event, and include the date if known.
- ***Life-threatening*** Report if suspected that the patient will be at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
- ***Hospitalization (initial or prolonged)*** Report if admission to the hospital or prolongation of hospitalization will be a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- ***Disability or Permanent Damage*** Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

- ***Congenital Anomaly/Birth Defect*** Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- ***Required Intervention to Prevent Permanent Impairment or Damage (Devices)*** Report if you believe that medical or surgical intervention will be necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- ***Other Serious (Important Medical Events)*** Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.
- ***Complications related to TIPS*** TIPS dysfunction, thrombosis, occlusion/stenosis transcapsular puncture, intraperitoneal bleed, hepatic infarction, fistulae,hemobilia, sepsis,,infection of tips, hemolysis, encephalopathy, stent migration or placement into ivc or too far into portal vein
- ***Complications related to endoscopic therapy:*** esophageal stenosis, esophageal ulcers, dysphasia,esophagitis
- ***Complications related to NSBB:*** dizziness,hypotension, bradycardia, fatigue, shortness of breath, diarrhoea

Sample size calculation

No study has yet compared the outcome between cirrhotic patients with PVT receiving TIPS and those receiving conventional therapy. The sample size was determined on the basis of the results of 12 RCTs in which the rate of variceal bleeding was compared between cirrhotic patients without PVT treated by TIPS and endoscopic therapy (**Table 1**) [33-44]. The pooled rates of variceal rebleeding are estimated to be 20.0% and 43.4% in the TIPS and endoscopic therapy groups, respectively. Notably, bare stents were employed in these 12 RCTs, but covered stents will be used in our study.

Table 1. The rates of variceal rebleeding in cirrhotic patients without portal vein thrombosis treated by TIPS or endoscopic therapy: A review of 12 randomized controlled trials.

First author (*Journal, Year*)	TIPS group		Endoscopy group	
	Total number of Pts.	Number of Pts. with variceal rebleeding (%)	Total number of Pts.	Number of Pts. with variceal rebleeding (%)
Cabrera (*Gastroenterology, 1996*)	31	7 (22.6%)	32	16 (50%)
Cello (*Ann Intern Med, 1997*)	24	3 (14.3%)	26	12 (46.2%)
Jalan (*Hepatology, 1997*)	31	3 (9.7%)	27	14 (51.9%)
Rossle (*Lancet, 1997*)	61	15 (24.6%)	65	33 (50.8%)
Sanyal (*Ann Intern Med, 1997*)	41	10 (24.4%)	39	10 (25.6%)
Sauer (*Gastroenterology, 1997*)	42	6 (14.3%)	41	21 (51.2%)
Merli (*Hepatology, 1998*)	38	9 (23.7%)	43	22 (51.2%)
Garica-Villarreal (*Hepatology, 1999*)	22	2 (9.1%)	24	12 (50%)
Narahara (*Hepatol Res, 2001*)	38	7 (18.4%)	40	13 (32.5%)
Pomier-Layrargues (*Gut, 2001*)	41	8 (19.5%)	39	22 (56.4%)
Sauer (*Endoscopy, 2002*)	43	8 (18.6%)	42	13 (31%)
Gulberg (*Scand J Gastroenterol, 2002*)	28	8 (28.6%)	26	6 (23.1%)

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.

Because the rate of shunt dysfunction is lower in patients with covered stents than in those with bare stents [45-46], the rate of variceal rebleeding should be lower in the patients allocated to the TIPS group in our study. On the other hand, given that the rate of variceal bleeding is significantly aggravated by the presence of portal vein thrombosis [5], the rate of variceal rebleeding might be higher in patients allocated to the Conventional Therapy group in our study. Thus, we presume that the rates of variceal rebleeding will be 10% and 45% in TIPS and Conventional Therapy groups, respectively. Considering a type I (α) error of 5%, a type II (1-β) error of 20%, and a dropout rate of 10%, the total number of patients to be recruited is 50.

Statistical analysis

All data will be analyzed on the intention-to-treat population. Continuous variables will be summarized as the mean values (± standard errors) or the median values (ranges), and will be compared using the independent sample t-test or one-way analysis of variance (ANOVA). Categorical variables will be expressed as frequencies, and will be compared using the Chi-square test or Fisher's exact test. Cumulative risks will be assessed with Kaplan-Meier curves, and will be compared using the log-rank test. The independent predictors for variceal rebleeding, death, and variceal bleeding-related death will be calculated using the Cox regression model. Two-tailed p-values <0.05 will be considered statistically significant. All statistical calculations will be performed using SPSS 12.0 (Chicago, Illinois, USA) and SAS 8.1 (Cary, North Carolina, USA).

Study implications

PVT increases the rate of variceal rebleeding and mortality in cirrhotic patients [5, 47], thereby negatively changing the natural history of advanced liver cirrhosis [48]. However, no randomized controlled studies have evaluated which treatment modality is preferable to prevent variceal rebleeding in cirrhotic patients with PVT. This study is the first RCT to explore the efficacy of TIPS and conventional therapy for the prevention of variceal rebleeding in such patients. Survival and portal vein recanalization will be compared between patients treated by TIPS and conventional therapy. If TIPS is superior to conventional therapy, TIPS might be recommended as the first-line therapy in these patients. This study will also provide information regarding the natural history of cirrhotic patients with PVT that cannot be recanalized.

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Transjugular intrahepatic portosystemic shunt for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: Study protocol for a randomized controlled trial

Background

Variceal bleeding is a common and serious complication of advanced liver cirrhosis [1-3]. The incidence of a first variceal bleeding within one year is about 12% in cirrhotic patients with gastro-esophageal varices [2-3]. The incidence of variceal rebleeding within one year is 60% in cirrhotic patients with a previous history of variceal bleeding, and the mortality from each rebleeding episode is nearly 20% [2-4]. The presence of portal vein thrombosis (PVT) further increases the incidence of variceal rebleeding in cirrhotic patients [5].

The current therapeutic algorithm for the secondary prophylaxis of variceal bleeding in liver cirrhosis includes non-selective beta-blockers (NSBBs) combined with endoscopic therapy (ET) as the first-line choice of therapy and TIPS as the second-line therapy [2-3, 6]. This recommendation is mainly because the rate of hepatic encephalopathy is significantly higher in patients undergoing TIPS than in those receiving NSBBs and ET, but the overall survival is not improved [7-9]. However, the therapeutic algorithm could not be readily extrapolated to cirrhotic patients with PVT.

On the other hand, the efficacies of anticoagulation therapy and transjugular intrahepatic portosystemic shunt (TIPS) for recanalizing PVT in liver cirrhosis have been shown in several case series [10-13]. However, the limitations of the two treatment modalities are clear. First, anticoagulation therapy appears to be effective for recanalizing partial PVT rather than complete PVT or cavernous transformation of the portal vein [14-15]. Second, if anticoagulation therapy was used in cirrhotic patients with a history of variceal bleeding, the risk or severity of bleeding might be further exacerbated [16-17]. Third, the TIPS technique in the presence of PVT is relatively difficult [18], and the procedure-related complications are potentially lethal [18-19]. Due to the absence of randomized controlled studies, no definite treatment algorithm for the management of variceal rebleeding in liver cirrhosis and PVT has been well established in the Baveno V consensus and recent American Association for the Study of Liver Diseases (AASLD) practice guidelines on the management of vascular disorders of the liver [20-21].

We hypothesize that TIPS may be superior to conventional therapy for the prevention of variceal rebleeding in liver cirrhosis patients with non-tumoral PVT [22]. Thus, a randomized controlled trial (RCT) is being conducted at our center to explore this issue.

Methods/Design

Study Design

This is a randomized controlled study evaluating TIPS versus conventional therapy (i.e., ET combined with NSBBs) for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT who had bled within the past 6 week.(**Figure 1**).

Cirrhotic patients with PVT presenting with an acute upper gastrointestinal bleed underwent emergency upper gastrointestinal endoscopy. Acute esophageal variceal bleed was diagnosed if active bleeding was seen from the varix, a white nipple or a clot was seen on the varix, or if there was blood in the stomach in a patient with an esophageal varix and no other potential bleeding source. If esophageal varices were found to be the cause of bleed, these patients underwent band ligation and also were given vasoactive drugs (terlipressin or somatostatin) for 5 days. Those patients who had a failure of primary hemostasis during acute bleed were excluded from the study. On day 6 of acute bleed, patients were screened and if found to satisfy the inclusion and exclusion criteria, were enrolled and randomly assigned to receive either endoscopic variceal ligation (EVL) +propranolol or TIPS for secondary prophylaxis. Thus, day 6 of acute bleed formed day 1 of randomization in patients presenting with acute bleed.

Those patients with PVT who presented with a history of recent bleed from esophageal varices and satisfying the inclusion and exclusion criteria were enrolled and randomized on day 1 to receive either TIPS or EVL + propranolol. Patients who previously had received more than one session of ligation/sclerotherapy were excluded.

All subjects who meet the entry criteria will be randomized at a ratio of 1:1 to receive either TIPS or conventional therapy. This study is being performed in the Departments of Liver Disease, Digestive Interventional Radiology, Endoscopy, and Ultrasound of Xijing Hospital of Digestive Diseases, Fourth Military Medical University.

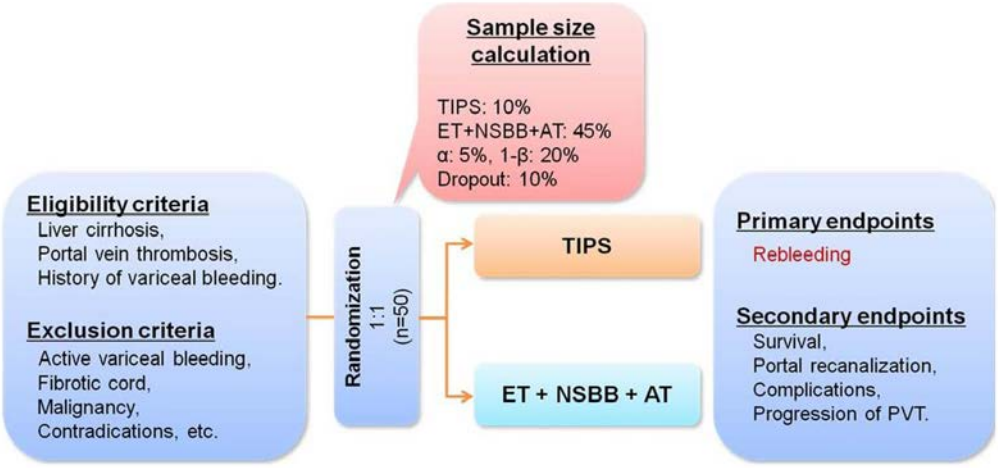

Figure 1 Study design.
Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic therapy; NSSB, non-selective beta blocker; AT, anticoagulation; PVT, portal vein thrombosis.

Inclusion criteria

1. Written informed consent.
2. Adult patients (aged 18-75 years old).
3. Diagnosis of liver cirrhosis (liver cirrhosis is diagnosed by clinical presentations, laboratory tests, images, and liver biopsies).
4. Diagnosis of PVT (axial computed tomography [CT] scans demonstrate that thrombus occupies >50% of the portal vein lumen with or without portal cavernoma).
5. History of variceal bleeding within the past 6 week (all subjects will undergo endoscopy to confirm that the upper gastrointestinal bleeding originates from the esophageal and gastric varices rather than other potential sources).

Exclusion criteria

1. Uncontrolled active variceal bleeding (the time frame of the acute bleeding episode should be 120 hours [18]).
2. The thrombosed portal trunk is progressed to the fibrotic cord (the patients will be included, if the interventional radiologists consider that the diameter of a collateral vessel is large enough to place a stent [8, 17]).
3. History of TIPS placement, shunt surgery or EVL +NSBB
4. Concomitant renal insufficiency.
5. Severe cardiopulmonary diseases.
6. Uncontrolled systemic infection or sepsis.
7. Malignancy or other serious medical illness that may reduce life expectancy.
8. Contraindications for propranolol.
9. Contraindications for heparin or warfarin.
10. Contraindications for TIPS.
11. Pregnant or breast-feeding subjects (before enrollment, human chorionic gonadotropin is measured in all female patients).

Informed consent

All relevant information regarding the clinical trial is included in informed consent forms in the Chinese language. Further, the investigators (HC, HG, YZ, and QX) will provide a detailed explanation of this trial to the eligible patients. Informed consent must be signed by all patients or their relatives if the informed consent cannot be signed by the patients themselves. All patients' personal data and medical information will be kept confidential. All patients will be permitted to withdraw from this trial at any time.

Randomization

After the eligible patients give informed written consent, they will be stratified according to the Child-Pugh class (Child-Pugh class A= 5-6 points, Child-Pugh class B= 7-9 points, Child-Pugh

class C= 10-15 points) [23] and the degree of PVT (partial obstruction, complete obstruction, obliterative portal vein) [8, 24]. The patients will then be randomized into the TIPS and Conventional Therapy groups using web-based allocation system (http://openrct.fmmu.edu.cn) with Pocock and Simon's minimisation method. This system has been established by two investigators (CH and XJ) from the Department of Statistics of the Fourth Military Medical University.

Intervention

TIPS group

Patients assigned to the TIPS group will undergo TIPS insertions within 48 hours of randomization. All procedures will be performed with patients under conscious sedation and local anaesthesia by the same experienced interventional team (GH, CH, ZY, and WG) in which an experienced interventional radiologist and hepatologist (GH) is the operator with one of the others serving as first assistant, and a fellow as second assistant. Generally, both contrast-enhanced computed tomography and indirect portography via the superior mesenteric artery are initially employed to evaluate the portal venous system in all patients. If the intrahepatic portal vein branches could be visualised, a conventional transjugular approach will be the first choice. When indirect portography revealed poor or no visualisation of the portal vein and its branches, an ultrasound-guided percutaneous transhepatic approach will be employed to facilitate the TIPS procedure. When access of the intrahepatic portal vein branch was not feasible or failed, an ultrasound-guided percutaneous transsplenic approach will be attempted [8, 17, 25].

Transjugular approach Under the fluoroscopic guidance, an 18-gauge RUPS-100 needle (Rosh-Uchida TIPS set, Cook, Bloomington, USA) will be introduced into the hepatic vein through a long 5-F vascular sheath inserted into the internal jugular vein and punctured through the liver parenchyma from the hepatic vein to the portal vein. When the portal vein is accessed, a hydrophilic guidewire (Terumo, Tokyo, Japan) is used to navigate thrombosed/stenotic segments of portal vein eventually accessing the patent portion of the portal or splenic vein. Next, a portal venogram was performed and the portosystemic pressure gradient (PSG) will be measured. If large varices were identified, coil embolization of esophagogastric varices was performed. The identified occluded portal vein and the intrahepatic tract is dilated using 8 mm/40 mm balloons (PowerFlex, Cordis, Tipperary, Ireland). A ePTFE covered stent (Fluency®, Bard Peripheral Vascular, Tempe, AZ, USA) with a diameter of 8 mm and a length of 6-10 cm will be placed with their proximal end at the hepatocaval junction and their distal end in a patent portion of the portal venous system.If the first stent does not maintain sufficient intra-stent flow, an additional stent will be deployed coaxially. If a large collateral vein was present in patients in whom portal vein recanalisation is not feasible, TIPS placement will be considered to drain blood flow from the large collateral vein to the hepatic vein. The stents will be initially dilated to maximum obtain a good gradient.Finally, the PSG will be remeasured and repeat portography was performed. If residual thrombus remains in the distal end of the stent, an indwelling venous catheter will be

placed in the confluence of the superior mesenteric vein and splenic vein for local thrombolysis with bolus infusions of urokinase (500,000 units twice a day) for 3 days. If the occluded main portal vein or superior mesenteric vein cannot be recanalized or TIPS insertion fails, the patients will be treated with conventional therapy. A Doppler ultrasound was carried out within 2-7 days to evaluate shunt patency.

A combined transjugular/transhepatic or transjugular/transsplenic approach Under ultrasound guidance, the intrahepatic portal vein branch or a suitable splenic vein near the splenic hilum will be punctured with an 18-G PTC needle by the same well-trained doctor (WJ). Then, a 0.035-inch hydrophilic guidewire (Terumo, Tokyo, Japan) will be advanced and a 5-Fr introducer sheath (Terumo,Tokyo, Japan) was placed. The guidewire and a 5-Fr Cobra catheter (Cordis, Florida, USA) will be employed to probe the occlusion and to traverse the occluded portal vein into the superior mesenteric or splenic vein**.** Once the occlusion is traversed, the catheter will be retracted back with its tip positioned at the site of desired portal vein access and the guidewire left in the SMV or SV. Under fluoroscopic guidance, the transjugular Rosch-Uchida needle will be used to puncture the tip of catheter which served as a target. After confirming the desired portal vein successful puncture, a transjugular guidewire will advance through the needle into the portal system. Then a classical TIPS procedure will be performed to reconstruct hepatopetal blood flow.Both the transhepatic and transsplenic tracts will be embolized with coils after TIPS.

After the TIPS insertions, intravenous infusions of heparin (8,000-12,000 u/d) for five days followed by oral warfarin for 6 months will be routinely prescribed at doses that achieve an international normalized ratio (INR) of up to two times the upper limit of normal for the prevention of shunt dysfunction. Intravenous antibiotics for 4-5 days will be prescribed for the prevention of operation-related infections. If any evidence of shunt dysfunction is observed, TIPS revision by balloon angioplasty and additional stent-placement will be planned. If the shunt dysfunction cannot be revised, the patients will be treated with conventional therapy.

Shunt dysfunction will be suspected in any one of the following conditions: (1) recurrent variceal bleeding; (2) recurrent or gradually worsening ascites; or (3) the maximum flow velocity within the shunt is less than 50 cm/s or the flow velocity within the shunt is absent on color Doppler ultrasound (CDUS). Suspected dysfunction will be further confirmed, if shunt stenosis is greater than 50% on portography and/or the PSG is beyond 12 mmHg[8].

Conventional Therapy group

ET. Patients assigned to the Conventional Therapy group will undergo endoscopic variceal ligation (EVL) within 48 hours of randomization. According to the AASLD practice guidelines for the management of variceal bleeding [3, 26], varices are ligated every 1-2 weeks until they are obliterated or are considered inappropriate for ligation by endoscopists. Endoscopic screening for recurrent varices is arranged within 1-3 months after variceal obliteration, and a repeat endoscopy is then conducted every 6 months. Recurrence of varices was defined as appearance or an increase in the grade of varices after achieving successful eradication or

reduction in size of varices. If varices reappeared, further EVL sessions were initiated.

NSSBs. Patients assigned to the Conventional Therapy group will receive NSSBs immediately after randomization. According to the AASLD practice guidelines for the management of variceal bleeding [3, 26], propranolol should be started at a dose of 20 mg twice a day, and is adjusted to the maximum tolerated dose (160 mg twice a day) or until the heart rate is reduced to 55 b.p.m or 25% from baseline.

Anticoagulation. Patients assigned to the Conventional Therapy group will receive anticoagulants within 2 weeks after variceal obliteration. According to the American College of Chest Physicians (ACCP) guidelines for the management of deep vein thrombosis [27], intravenous infusions of heparin are initially administered at a dose of 1,000 units per hour for 5 days. Subsequently, oral warfarin should be started at a dose of 2.5 mg once a day, and is adjusted to achieve an INR of up to two times the upper limit of normal. Oral warfarin therapy will continue for 6 months or until portal vein complete recanalization.

NSBBs-induced adverse events include lightheadedness, fatigue, and shortness of breath, while the anticoagulant-induced adverse events include bleeding, thrombocytopenia with or without thrombosis, osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, and hypoaldosteronism. If adverse events are considered mild or moderate, the treatment will be continued or the dose of these drugs will be reduced until they disappear. If adverse events are considered severe or the patients are unable to tolerate these drugs, the treatment will be discontinued.

TIPS rescue**.** Patients assigned to the Conventional Therapy group will receive TIPS as a rescue therapy in any one of the following conditions: (1) one episode of clinically significant variceal re-bleeding after endoscopic therapy resulting in the development of hypovolemic shock or a 3 g drop in hemoglobin within any 24 h period if no transfusion is administered [18]; (2) two episodes of clinically significant re-bleeding (i.e., melena or hematemesis); or (3) one episode of clinically significant re-bleeding with pampiniform or racemose varices on endoscopy that are considered inappropriate for ligation or sclerotherapy by endoscopists.

Objectives

Primary objective

To compare the rate of variceal rebleeding between the patients undergoing TIPS and those receiving endoscopic therapy combined with NSSBs and anticoagulants.

Secondary objectives

1. To compare the rate of overall death and variceal bleeding-related death between the two groups.
2. To compare the rate of portal vein recanalization between the two groups.

3. To compare the rate of complications between the two groups.
4. To observe the progression of PVT in patients without portal vein recanalization.

Data collection

Paper case report forms have been designed for data collection by one investigator.

Upon enrollment, the following data will be collected:

1. Demographic characteristics (sex and age).
2. Physical examination parameters (blood pressure, heart rate, height, weight, shifting dullness, hepatomegaly, and splenomegaly).
3. Disease history (the date of diagnosis of liver cirrhosis and PVT, the therapeutic methods of variceal bleeding, viral hepatitis, thrombosis at other sites, alcohol abuse, drug use, abdominal trauma and surgery, hematological disease, the use of oral contraceptives, and other diseases).
4. Laboratory tests (red blood cells, hemoglobin, white blood cells, platelets, total bilirubin, direct and indirect bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glutamine transferase, urea nitrogen, serum creatinine, potassium, sodium, alpha-fetoprotein, prothrombin time, INR, and D-dimer).
5. Electrocardiogram.
6. Anteroposterior chest radiographs.
7. Abdominal CDUS (liver, spleen, grade of ascites [28], and the extension and degree of PVT [24]).
8. Abdominal CT scans (liver, spleen, grade of ascites, and the extension and degree of PVT).
9. Upper gastrointestinal endoscopy (the location, form, and diameter of the varices and red color signs).
10. Child-Pugh [23] and Model for End-stage Liver Disease (MELD) scores [29].

As the patients are allocated into the TIPS group, the following data will be collected:

1. The overall duration of the TIPS procedure.
2. Approaches used for the percutaneous puncture of the portal vein (transjugular, trans-hepatic, and trans-splenic approaches).
3. Whether coil embolization of varices is performed.
4. The number of coils if embolization is performed.
5. The number of TIPS stents.
6. Whether local thrombolysis is performed after stent placement.
7. The PSG before and after TIPS.
8. TIPS procedure-related complications (i.e., hepatic capsule perforation, stent displacement).
9. Whether TIPS revision is performed.
10. The number, duration, and methods (additional stent-placement and/or balloon angioplasty) of TIPS revision(s) if TIPS revision is performed.

As the patients are allocated into the Conventional Therapy group, the following data will

be collected:

1. The overall duration of endoscopic therapy.
2. The number of sessions required to eradicate the varices.
3. The number of bands and volume of sclerosant and glue.
4. Endoscopic therapy-related complications.
5. The dose of propranolol used for adequate beta blockade.
6. Heart rate at the time of adequate beta blockade.
7. Whether propranolol is discontinued.
8. The dose of warfarin used as the target INR is achieved.
9. Whether warfarin is discontinued.
10. Adverse events of propranolol and warfarin.

A regular follow-up flow chart will be established (**Figure 2**). The grade of varices will be evaluated by endoscopy. The Child-Pugh and MELD scores will be calculated. The extension and degree of PVT will be evaluated by abdominal CDUS and CT scans. According to previous studies [7, 30-31], **portal vein recanalization** is considered **complete** if the portal vein trunk, superior mesenteric vein, and splenic vein are patent; **portal vein recanalization** is considered **partial** if the degree of thrombosis within the portal vein trunk is decreased. Additionally, all enrolled patients will have telephone follow up with one investigator (WZ) regarding their conditions and drug use every week in the first month and once per month thereafter.

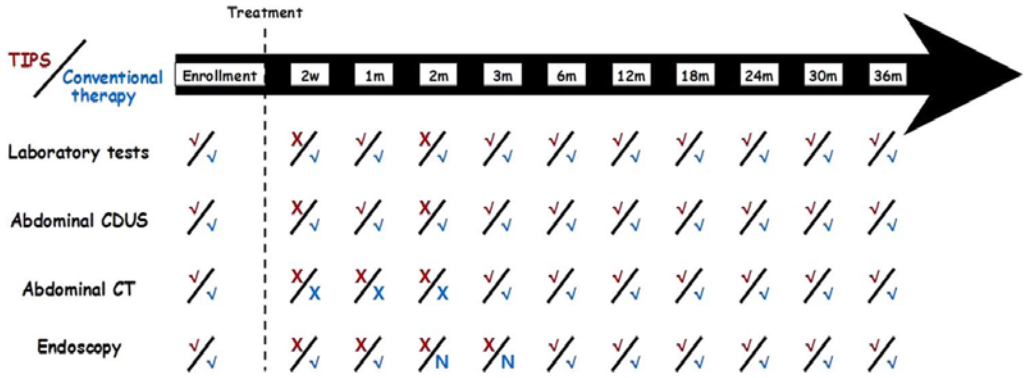

Figure 2 Regular follow-up flow chart.
Notes: √, performed; X, not performed; N, performed if necessary.
Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; CT, computed tomography; CDUS, color Doppler ultrasound.

As hepatic encephalopathy occurs, the following data will be collected:

1. The number of episodes of hepatic encephalopathy.
2. The starting time and duration of every episode of hepatic encephalopathy.
3. The grade of every episode of hepatic encephalopathy according to the West Haven Criteria [32].
4. The treatment and outcome of every episode of hepatic encephalopathy.

As shunt dysfunction occurs, the following data will be collected:

1. The number of episodes of shunt dysfunction.
2. The starting time and duration of every episode of shunt dysfunction.
3. The diagnosis, treatment, and outcome of every episode of shunt dysfunction.

As variceal bleeding recurs, the following data will be collected:

1. The number of variceal rebleeds.
2. The starting time and duration of every episode of variceal rebleeding.
3. The causes of every episode of variceal rebleeding.
4. The treatment and outcome of every episode of variceal rebleeding.

As any patient dies, the following data will be collected:

1. The time of death after enrollment.
2. The cause of death.

Reporting of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious adverse event (SAE) must be reported to the regulatory authorities immediately (within 24h), whereas **non-serious adverse events** are merely documented in the annual summary sent to the regulatory authority.

Serious adverse event is defined as any untoward medical occurrence when the patient outcome is:

1. **Death** Report if you suspect that the death will be an outcome of the adverse event, and include the date if known.
2. **Life-threatening** Report if suspected that the patient will be at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
3. **Hospitalization (initial or prolonged)** Report if admission to the hospital or prolongation of hospitalization will be a result of the adverse event.
4. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
5. **Disability or Permanent Damage** Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
6. **Congenital Anomaly/Birth Defect** Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse

outcome in the child.

7. **Required Intervention to Prevent Permanent Impairment or Damage (Devices)** Report if you believe that medical or surgical intervention will be necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
8. **Other Serious (Important Medical Events)** Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Complication related to treatment

- ***Complications related to TIPS*** TIPS dysfunction, thrombosis, occlusion/stenosis transcapsular puncture, intraperitoneal bleed, hepatic infarction, fistulae,hemobilia, sepsis,,infection of TIPS, hemolysis, encephalopathy, stent migration or placement into IVC or too far into portal vein

- ***Complications related to endoscopic therapy:*** esophageal stenosis, esophageal ulcers, dysphasia,esophagitis

- ***Complications related to NSBB:*** dizziness, hypotension, bradycardia, fatigue, shortness of breath, diarrhoea

Sample size calculation

No study has yet compared the outcome between cirrhotic patients with PVT receiving TIPS and those receiving conventional therapy. The sample size was determined on the basis of the results of 12 RCTs in which the rate of variceal bleeding was compared between cirrhotic patients without PVT treated by TIPS and endoscopic therapy (**Table 1**) [33-44]. The pooled rates of variceal rebleeding are estimated to be 20.0% and 43.4% in the TIPS and endoscopic therapy groups, respectively. Notably, bare stents were employed in these 12 RCTs, but covered stents will be used in our study.

Table 1. The rates of variceal rebleeding in cirrhotic patients without portal vein thrombosis treated by TIPS or endoscopic therapy: A review of 12 randomized controlled trials.

First author (*Journal, Year*)	TIPS group		Endoscopy group	
	Total number of Pts.	Number of Pts. with variceal rebleeding (%)	Total number of Pts.	Number of Pts. with variceal rebleeding (%)
Cabrera (*Gastroenterology, 1996*)	31	7 (22.6%)	32	16 (50%)
Cello (*Ann Intern Med, 1997*)	24	3 (14.3%)	26	12 (46.2%)
Jalan (*Hepatology, 1997*)	31	3 (9.7%)	27	14 (51.9%)
Rossle (*Lancet, 1997*)	61	15 (24.6%)	65	33 (50.8%)
Sanyal (*Ann Intern Med, 1997*)	41	10 (24.4%)	39	10 (25.6%)
Sauer (*Gastroenterology, 1997*)	42	6 (14.3%)	41	21 (51.2%)
Merli (*Hepatology, 1998*)	38	9 (23.7%)	43	22 (51.2%)
Garica-Villarreal (*Hepatology, 1999*)	22	2 (9.1%)	24	12 (50%)
Narahara (*Hepatol Res, 2001*)	38	7 (18.4%)	40	13 (32.5%)
Pomier-Layrargues (*Gut, 2001*)	41	8 (19.5%)	39	22 (56.4%)
Sauer (*Endoscopy, 2002*)	43	8 (18.6%)	42	13 (31%)
Gulberg (*Scand J Gastroenterol, 2002*)	28	8 (28.6%)	26	6 (23.1%)

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.

Because the rate of shunt dysfunction is lower in patients with covered stents than in those with bare stents [45-46], the rate of variceal rebleeding should be lower in the patients allocated to the TIPS group in our study. On the other hand, given that the rate of variceal bleeding is significantly aggravated by the presence of portal vein thrombosis [5], the rate of variceal rebleeding might be higher in patients allocated to the Conventional Therapy group in our study. Thus, we presume that the rates of variceal rebleeding will be 10% and 45% in TIPS and Conventional Therapy groups, respectively. Considering a type I (α) error of 5%, a type II (1-β) error of 20%, and a dropout rate of 10%, the total number of patients to be recruited is 50.

Statistical analysis

All data will be analyzed on the intention-to-treat population and supplemented by per-protocol (PP) principles and “as-treated” analysis. In the “as-treated” analysis, patients were analyzed according to the treatment regimen that they received. In addition to the censoring time points in the ITT analysis, patients were censored at the moment they switched therapy. Continuous variables will be summarized as the mean values (± standard errors) or the median values (ranges), and will be compared using the independent sample t-test or one-way analysis of variance (ANOVA). Categorical variables will be expressed as frequencies, and will be compared using the Chi-square test or Fisher’s exact test. Cumulative risks will be assessed with Kaplan-Meier curves, and will be compared using the log-rank test. The independent predictors for variceal rebleeding, death, and variceal bleeding-related death will be calculated using the Cox regression model. Two-tailed p-values <0.05 will be considered statistically significant. All statistical calculations will be performed using SPSS 18.0 (Chicago, Illinois, USA) and SAS 8.1 (Cary, North Carolina, USA).

Study implications

PVT increases the rate of variceal rebleeding and mortality in cirrhotic patients [5, 47], thereby negatively changing the natural history of advanced liver cirrhosis [48]. However, no randomized controlled studies have evaluated which treatment modality is preferable to prevent variceal rebleeding in cirrhotic patients with PVT. This study is the first RCT to explore the efficacy of TIPS and conventional therapy for the prevention of variceal rebleeding in such patients. Survival and portal vein recanalization will be compared between patients treated by TIPS and conventional therapy. If TIPS is superior to conventional therapy, TIPS might be recommended as the first-line therapy in these patients. This study will also provide information regarding the natural history of cirrhotic patients with PVT that cannot be recanalized.

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Summary of changes

1. Any drug planned for encephalopathy prophylactics (arginine, branched-chain amino acids, L-ornithine-L-aspartate) and oral aspirin will not be used in TIPS group because their efficacy is not definite.

2. The time of NSSB administration change from “within 5–7 days after endoscopic therapy” to “immediately after randomization” according to current guidelines.

3. The endoscopic sclerotherapy and cyanoacrylate was abandoned in conventional therapy group.

Statistical Analysis Plan (original version)

Statistical analysis

All data will be analyzed on the intention-to-treat population. Continuous variables will be summarized as the mean values (± standard errors) or the median values (ranges), and will be compared using the independent sample t-test or one-way analysis of variance (ANOVA). Categorical variables will be expressed as frequencies, and will be compared using the Chi-square test or Fisher's exact test. Cumulative risks will be assessed with Kaplan-Meier curves, and will be compared using the log-rank test. The independent predictors for variceal rebleeding, death, and variceal bleeding-related death will be calculated using the Cox regression model. Two-tailed p-values <0.05 will be considered statistically significant. All statistical calculations will be performed using SPSS 18.0 (Chicago, Illinois, USA) and SAS 8.1 (Cary, North Carolina, USA).

Statistical Analysis Plan (Final version)

Statistical analysis

All data will be analyzed on the intention-to-treat population and supplemented by per-protocol (PP) principles and “as-treated” analysis. In the “as-treated” analysis, patients were analyzed according to the treatment regimen that they received. In addition to the censoring time points in the ITT analysis, patients were censored at the moment they switched therapy. Continuous variables will be summarized as the mean values (± standard errors) or the median values (ranges), and will be compared using the independent sample t-test or one-way analysis of variance (ANOVA). Categorical variables will be expressed as frequencies, and will be compared using the Chi-square test or Fisher’s exact test. Cumulative risks will be assessed with Kaplan-Meier curves, and will be compared using the log-rank test. The independent predictors for variceal rebleeding, death, and variceal bleeding-related death will be calculated using the Cox regression model. Two-tailed p-values <0.05 will be considered statistically significant. All statistical calculations will be performed using SPSS 18.0 (Chicago, Illinois, USA) and SAS 8.1 (Cary, North Carolina, USA).

Summary of changes

That “All data will be analyzed on the intention-to-treat population” change to “all data will be analyzed on the intention-to-treat population and supplemented by per-protocol (PP) principles and “as-treated” analysis”.