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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 randomised controlled trial

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ABSTRACT

Introduction: Portal vein thrombosis (PVT) increases the risk of variceal rebleeding in liver cirrhosis. However, the strategy for preventing variceal rebleeding in cirrhotic patients with PVT has not been explored. This study aims to evaluate whether the transjugular intrahepatic portosystemic shunt (TIPS) or conventional therapy is preferable for the prevention of variceal rebleeding in liver cirrhosis patients with PVT.

Methods and analysis: This is a randomised controlled trial comparing the safety and efficacy of TIPS versus conventional therapy (ie, endoscopic therapy combined with non-selective β-blockers and anticoagulants) for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT. A total of 50 cirrhotic patients with PVT (thrombus >50% of portal vein lumen occupancy) and a history of variceal bleeding will be stratified according to the Child-Pugh class and degree of PVT, and randomised into the TIPS and conventional therapy groups. The primary objective was to compare the incidence of variceal rebleeding between the two groups. The secondary objectives were to compare the overall mortality, variceal rebleeding-related mortality, portal vein recanalisation and complications between the two groups, and to observe the progression of PVT in patients without portal vein recanalisation.

Ethics and dissemination: This study was approved by the ethics committee of Xijing hospital (No. 20110224-5), and was registered at ClinicalTrials.gov (NCT01326949). All participants give written informed consent. The first patient was recruited into our study on 4 June 2011. A total of 29 patients were recruited through 5 March 2013 (14 and 15 patients assigned to the TIPS and conventional therapy groups, respectively). If TIPS is superior to conventional therapy for the prevention of variceal rebleeding in cirrhotic patients with PVT, TIPS might be recommended as the first-line therapy in such patients. But a small sample size potentially limits the generalisation of our conclusions.

Trial registration: This study was registered at ClinicalTrials.gov on 29 March 2011. The trial registration number is NCT01326949.

Trial status: The first patient was recruited into our study on 4 June 2011. A total of 29 patients were recruited through 5 March 2013 (14 and 15 patients assigned to the TIPS and conventional therapy groups, respectively).

INTRODUCTION

Variceal bleeding is a common and serious complication of advanced liver cirrhosis.[1–3] The incidence of a first variceal bleeding within 1 year is about 12% in cirrhotic patients with gastro-oesophageal varices.[2 3] The incidence of variceal rebleeding within 1 year is 60% in cirrhotic patients with a 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 efficacies of anticoagulation therapy and the transjugular intrahepatic portosystemic shunt (TIPS) for recanalising PVT in liver cirrhosis have been shown in several case series.[6–11] However, the limitations of the two treatment modalities are clear. First, anticoagulation therapy appears to be effective for recanalising partial PVT rather than complete PVT or cavernous transformation of the portal vein.[12 13] 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.[14 15] Third, the TIPS technique in the

presence of PVT is relatively difficult,[16] and the procedure-related complications are potentially lethal.[17] Owing to the absence of randomised controlled studies, no definite treatment algorithm for the management of PVT in liver cirrhosis 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.[18 19]

On the other hand, the current therapeutic algorithm for the secondary prophylaxis of variceal bleeding in liver cirrhosis includes non-selective β-blockers (NSBBs) combined with endoscopic therapy (ET) as the first-line choice of therapy and TIPS as the second-line therapy.[2 3 18] 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.[20 21] However, the therapeutic algorithm could not be readily extrapolated to cirrhotic patients with PVT.

We hypothesise 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 randomised controlled trial (RCT) is being conducted at our centre to explore this issue.

METHODS

Study design

This is a randomised controlled study evaluating TIPS versus conventional therapy (ie, ET combined with NSBBs and anticoagulants) for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT (figure 1). All patients who meet the entry criteria will be randomised 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.

Inclusion criteria

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

Exclusion criteria

1. Active variceal bleeding (the time frame of the acute bleeding episode should be 120 h[18]).
2. Thrombus occupies <50% of the portal vein lumen.
3. 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]).
4. History of TIPS placement or shunt surgery (the patients will be included if the surgical shunt is completely occluded or invalid).
5. Concomitant renal insufficiency (serum creatine level is 1.5-fold beyond the upper limit of normal (ie, >170 μmol/L)).
6. Severe liver insufficiency (the serum alanine aminotransferase or aspartate aminotransferase level is threefold beyond the upper limit of normal (ie, >120 U/L); or the total bilirubin level is threefold beyond the upper limit of normal (ie >60 μmol/L)).
7. Severe cardiopulmonary diseases.
8. Uncontrolled systemic infection or sepsis.
9. Malignancy or other serious medical illness that may reduce life expectancy.
10. Contraindications for propranolol.
11. Contraindications for heparin or warfarin.

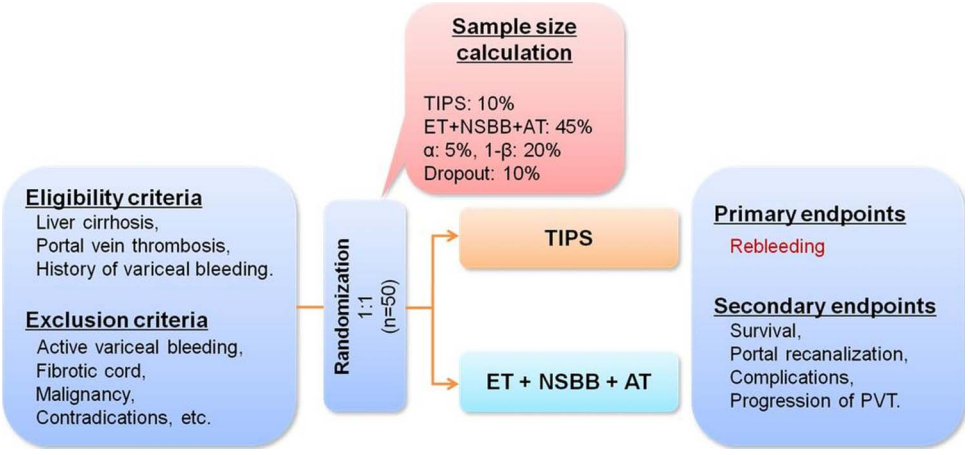

Figure 1 Study design. AT, anticoagulation; ET, endoscopic therapy; NSSB, non-selective β blocker; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

12. Absolute contraindications for TIPS (ie, congestive heart failure, multiple hepatic cysts, unrelieved biliary obstruction and severe pulmonary hypertension).[16]
13. HIV infection (before enrolment, HIV Ag/Ab is measured in all patients).
14. Pregnant or breastfeeding patients (before enrolment, human chorionic gonadotropin is measured in all female patients).
15. Patients 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 (CH, GH, ZY and/or XQ) 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.

Randomisation

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 Child-Pugh score is calculated based on the five clinical and laboratory variables (serum total bilirubin: <30 μmol/L=1 point, 30–50 μmol/L=2 points, >50 μmol/L=3 points; serum albumin: >35 g/L=1 point; 28–35 g/L=2 points, <28 g/L=3 points; international normalised ratio (INR): <1.70=1 point, 1.71–2.20=2 points, >2.20=3 points; ascites: no=1 point, mild=2 points, moderate or severe=3 points; encephalopathy: no=1 point, grade I-II=2 points, grade III-IV=3 points). Degree of PVT is evaluated based on the contrast-enhanced CT scans findings (partial obstruction: beyond half of the portal vein lumen occupancy; complete PVT: nearly entire portal vein lumen occupancy; obliterative portal vein: main portal vein disappears or progresses into a fibrotic cord). The patients will then be randomised into the TIPS and conventional therapy groups by means of a central randomisation system (http://openrct.fmmu.edu.cn). This system has been established by two investigators (HC and JX) from the Department of Statistics of the Fourth Military Medical University.

TIPS group

Patients assigned to the TIPS group will undergo TIPS insertions within 48 h of randomisation. A step-wise TIPS strategy has been described in our previous studies.[8 17 25] As Viatorr-covered stents are not approved by the State Food and Drug Administration in the Chinese mainland, Fluency covered stents (Bard Peripheral Vascular, Bard, Inc) with a diameter of 8 mm and a length of 6–10 cm will be employed in our study. If the residual thrombus remains at 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. Preoperative and postoperative portosystemic pressure gradients (PSGs) will be measured. If the occluded main portal vein or superior mesenteric vein cannot be recanalised or the TIPS insertion fails, the patients will be treated with conventional therapy.

After the TIPS insertions, intravenous infusions of heparin (50 mg twice a day) for 5–7 days followed by oral warfarin for 6–12 months will be routinely prescribed at doses that achieve an INR of up to two times the upper limit of normal for the prevention of shunt dysfunction. Intravenous L-ornithine-L-aspartate (20 g once a day) with or without branched-chain amino acids for 4–5 days will be administered for the prevention of portosystemic encephalopathy. 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, and thereafter, long-term anticoagulation will be prescribed. If the shunt dysfunction cannot be revised, the patients will be treated with conventional therapy.

As we have described previously,[8] 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 colour Doppler ultrasound (CDUS). Suspected dysfunction will be further confirmed if shunt stenosis is greater than 50% on portography and/or PSG is beyond 15 mm Hg.

Conventional therapy group

ET: Patients assigned to the conventional therapy group will undergo ET within 48 h of randomisation. According to the Baveno V and AASLD practice guidelines for the management of variceal bleeding,[3 18 26] varices are ligated every 1–2 weeks until they are obliterated or are considered inappropriate for ligation by endoscopists. Endoscopic sclerotherapy and/or cyanoacrylate glue injection are employed for gastric varices. Endoscopic screening for recurrent varices is arranged within 1–3 months after variceal obliteration, and a repeat endoscopy is then conducted every 6 months.

NSSBs: Patients assigned to the conventional therapy group will receive NSSBs within 5–7 days after ET. 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 be adjusted to the maximum tolerated dose (160 mg twice a day) or until the heart rate is reduced to 55 bpm 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 1000 units/h for 5 days. Subsequently, oral warfarin should be started at a dose of 2.5 mg once a day and be adjusted to achieve an INR of up to two times the upper limit of normal or a target INR range 2–3. Oral warfarin therapy will continue for 6–12 months.

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 the 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 the 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 rebleeding after ET resulting in the development of hypovolaemic shock or a 3 g drop in haemoglobin within any 24 h period if no transfusion is administered[18]; (2) two episodes of clinically significant rebleeding (ie, melena or haematemesis) or (3) one episode of clinically significant rebleeding with pampiniform or racemose varices on endoscopy that are considered inappropriate for ligation or sclerotherapy by endoscopists.

Primary objective

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

Secondary objectives

1. To compare the rate of overall death and variceal bleeding-related death between the two groups (subgroup analyses will be performed according to the Child-Pugh class and grade of PVT).
2. To compare the rate of portal vein recanalisation between the two groups (subgroup analyses will be performed according to the Child-Pugh class and grade of PVT).
3. To compare the rate of procedure-related complications between the two groups.
4. To compare the rate of hepatic encephalopathy after treatment between the two groups.
5. To evaluate the rate of shunt dysfunction in the TIPS group.
6. To observe the progression of PVT in patients without portal vein recanalisation.

Data collection

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

Upon enrolment, 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, haematological disease, the use of oral contraceptives and other diseases).
4. Laboratory tests (red blood cells, haemoglobin, 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, α-fetoprotein, prothrombin time, INR and D-dimer).
5. ECG.
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 colour signs).
10. The 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 embolisation of varices is performed.
4. The number of coils if embolisation is performed.
5. The number of TIPS stents.
6. Whether local thrombolysis is performed after stent placement.
7. PSG before and after TIPS.
8. TIPS procedure-related complications (ie, 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 ET.
2. The number of sessions required to eradicate the varices.

3. The methods of ET (ie, variceal ligation, sclerotherapy and cyanoacrylate glue injection).
4. The number of bands and volume of sclerosant and glue.
5. ET-related complications.
6. The dose of propranolol used for adequate β-blockade.
7. Heart rate at the time of adequate β-blockade.
8. Whether propranolol is discontinued.
9. The dose of warfarin used as the target INR is achieved.
10. Whether warfarin is discontinued.
11. 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 recanalisation is considered complete if the portal vein trunk, superior mesenteric vein and splenic vein are patent; portal vein recanalisation 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.

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 enrolment.
2. The cause of death.

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 ET (table 1).[33–44] The pooled rates of variceal rebleeding are estimated to be 20% and 43.4% in the TIPS and ET groups, respectively. Notably, bare stents were employed in these 12 RCTs, but covered stents will be used in our study.

As 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 PVT,[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 the 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 analysed on the intention-to-treat population. Continuous variables will be summarised as the mean values (±SEs) or the median values (ranges), and

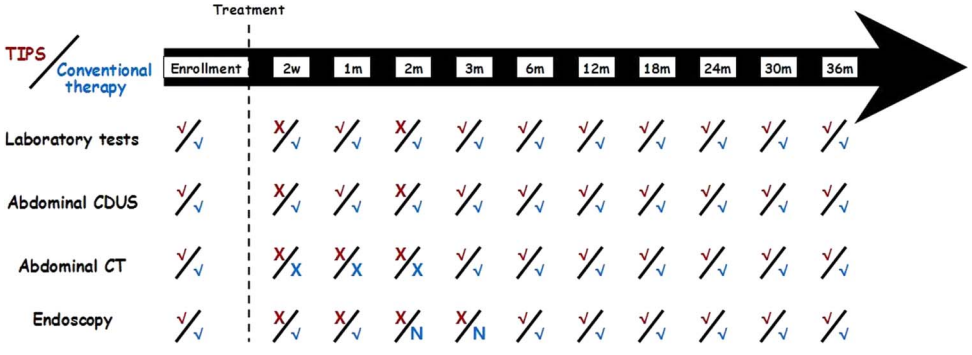

Figure 2 Regular follow-up flow chart. Notes: √, performed; X, not performed; N, performed if necessary. CDUS, colour Doppler ultrasound; TIPS, transjugular intrahepatic portosystemic shunt.

Table 1 Rates of variceal rebleeding in cirrhotic patients without portal vein thrombosis treated by TIPS or endoscopic therapy: a review of 12 randomised controlled trials

	TIPS group		Endoscopy group	
First author (Journal, Year)	Total number of patients	Number of patients with variceal rebleeding (%)	Total number of patients	Number of patients 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)

TIPS, transjugular intrahepatic portosystemic shunt.

will be compared using the independent sample t test or one-way analysis of variance. Categorical variables will be expressed as frequencies and compared using the χ^2 or Fisher's exact tests. Cumulative risks will be assessed with the Kaplan-Meier curves and 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 V.12.0 (Chicago, Illinois, USA) and SAS V.8.1 (Cary, North Carolina, USA).

DISCUSSION

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 randomised 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 recanalisation 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 recanalised.

Study limitations

First, cirrhotic patients with PVT are our target population. However, the sample size was calculated according to the previous results observed in cirrhotic patients without PVT. Therefore, the number of patients to be recruited in our study may be inadequate. Second, because the primary endpoint is variceal rebleeding, the power calculation is primarily based on a difference in the rate of variceal rebleeding between both groups. Thus, the data regarding mortality should not be overemphasised. Third, this study is being conducted in a single centre with the TIPS technique experience. Accordingly, our findings might not be promptly generalised to other centres with less experience. However, it should be noted that an increasing trend in the number of PVT patients undergoing TIPS has been clearly identified.[17] Fourth, the most common cause of liver cirrhosis is hepatitis B virus in China, while it is alcohol abuse in Western countries. The difference in the aetiology of liver cirrhosis might influence the application of our findings in Western countries. Fifth, the 'TIPS rescue' therapy may potentially increase the survival of patients assigned to the conventional therapy group. Thus, the difference in the mortality between the two treatment modalities cannot be truly reflected. Sixth, we did not clearly define the maximum interval from the last episode of variceal bleeding to our randomisation. Considering that a longer interval might be associated with a better survival, the absence of the threshold might produce a bias of patient selection. Certainly, this selection bias might be minimised due to the nature of randomisation.

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Contributors XQ participated in the study conception and design, patient randomisation, data collection, drafting of the study hypothesis, informed consent and study protocol, and critical revision of the manuscript. CH participated in the study design, patient recruitment, patient administration, TIPS surgery, follow-up and critical revision of the manuscript. ZY participated in the study design, TIPS surgery, patient administration, follow-up and critical revision of the manuscript. ZW participated in the data collection, telephone follow-up and regular follow-up. HZ and LY participated in the study design and endoscopic therapy. JW participated in the study design, percutaneous puncture of the portal vein under ultrasound-guided trans-hepatic and trans-splenic approaches and ultrasound follow-up of patients. JX and HC participated in the study design, establishment of the central randomisation system and the statistical analysis plan. ZY and MB participated in the study design and critical revision of the manuscript. WG participated in the study design and TIPS surgery. JN participated in the data collection and regular follow-up. KW and DF participated in the study supervision, study design, critical revision of the manuscript and funds collection. GH participated in the study supervision, study conception and design, patient recruitment, patient administration, TIPS surgery, follow-up, critical revision of the manuscript and funds collection. All authors gave final approval of the version to be published.

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Competing interests None.

Ethics approval This study was approved by the ethics committee of Xijing Hospital on 24 February 2011. The ethical approval number is No. 20110224-5.

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