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Hypothesis

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Transjugular intrahepatic portosystemic shunt may be superior to conservative therapy for variceal rebleeding in cirrhotic patients with non-tumoral portal vein thrombosis: A hypothesis

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

The presence of occlusive portal vein thrombosis (PVT) greatly changes the natural history of liver cirrhosis, because it not only significantly increases the incidence of variceal rebleeding but also negatively influences the survival. However, due to the absence of strong evidence, no standard treatment algorithm for the secondary prophylaxis of variceal bleeding in cirrhotic patients with non-tumoral PVT has been established.

Previous randomized controlled trials have demonstrated that transjugular intrahepatic portosystemic shunt (TIPS) can significantly decrease the incidence of variceal rebleeding in cirrhotic patients without PVT, compared with conservative therapy (i.e., endoscopic plus pharmacological therapy). Further, several large cohort studies have confirmed that TIPS can effectively prevent variceal rebleeding in cirrhotic patients with non-tumoral PVT. On the other hand, TIPS can facilitate recanalizing the thrombosed portal vein by endovascular manipulations, even in the presence of cavernous transformation of the portal vein (CTPV). More importantly, successful TIPS insertions can maintain the persistent portal vein patency, and avoid thrombus extension into the portal venous system. By comparison, anticoagulation therapy can achieve portal vein recanalization only in patients with partial PVT, but not in those with occlusive PVT or CTPV, and the use of anticoagulants may aggravate the risk of variceal bleeding in cirrhotic patients with a history of variceal bleeding.

Collectively, we hypothesize that TIPS may be superior to conservative therapy for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT. Randomized controlled trials should be conducted to evaluate the survival benefit of TIPS in these patients.

key words: transjugular intrahepatic portosystemic shunt • variceal bleeding • liver cirrhosis • portal vein thrombosis • anticoagulation • endoscopic therapy

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Background

Portal vein thrombosis (PVT) refers to thrombosis within the portal vein trunk, with or without thrombus extension to the intrahepatic portal vein branches, the splenic or mesenteric veins [1,2]. The prevalence of PVT in cirrhotic patients is 10–25% [3,4], and its incidence is approximately 8–16% [5–7]. The most important precipitating factor to the development of non-tumoral PVT in cirrhotic patients is the decreased velocity and stagnation of portal blood flow [7]. In addition, both inherited coagulation disorders (such as factor V Leiden mutation, factor II G20210A mutation, and C677T mutation in the 5,10-methylenetetrahydrofolate reductase [MTHFR]) and hypercoagulability (such as increased levels of factor VIII and decreased levels of protein C, protein S and antithrombin III) play a role in the pathogenesis of PVT in patients with liver cirrhosis [5,8–10]. Notably, it has been proposed that the presence of occlusive PVT potentially changes the natural history of liver cirrhosis [11,12] because it not only significantly increases the incidence of variceal rebleeding but also decreases the patients' survival [13,14]. Accordingly, it is of great value to learn how to prevent and treat non-tumoral PVT and complications of portal hypertension in cirrhotic patients. This paper aims to review the status quo of management of non-tumoral PVT and variceal rebleeding in cirrhotic patients, and to establish a hypothesis to evaluate which treatment modality is superior in these patients.

Current Recommendations for the Treatment of Non-Tumoral PVT in Cirrhosis

In the Baveno V consensus and recent American Association for the Study of Liver Diseases (AASLD) practice guidelines, due to the absence of randomized controlled studies [15,16] no definite treatment algorithm for the management of non-tumoral PVT in liver cirrhosis has been established.

Given the role of inherited coagulation disorders and hypercoagulability in the pathogenesis of PVT in liver cirrhosis, it seems to be theoretically reasonable that anticoagulation therapy should be used for recanalizing the thrombosed portal veins in cirrhotic patients. To date, several case series have shown a relatively high portal venous recanalization rate (42–82%) in cirrhotic patients with PVT receiving anticoagulation therapy [6,17,19]. However, the characteristics of the patients included in these studies were potentially biased, as follows: 1. most of the included patients presented with partial PVT; 2. only a minority of the included patients presented with complete PVT; and 3. all patients with cavernous transformation of the portal vein (CTPV) were excluded as potential candidates receiving anticoagulation [20]. Indeed, it is very difficult to recanalize the completely occluded portal vein by using anticoagulants alone in cirrhotic patients. In a recent study, 24 patients with PVT received anticoagulants before liver transplantation, and 21 and 3 of them presented with partial and complete occlusion, respectively [21]. Portal vein recanalization was achieved in 15 of 21 patients with partial PVT, but in none of the patients with complete PVT [21]. These findings strongly indicate that anticoagulants might be useless in recanalizing occlusive PVT. Thus, as occlusive PVT could not be recanalized by anticoagulation, it may further progress into the fibrotic cord [22,23], thereby increasing the cirrhotic patients' mortality [24] and the technical difficulty of liver transplantation [25]. Additionally, if anticoagulation was used in cirrhotic patients with medium or large esophageal varices and a history of variceal bleeding, the risk or severity of bleeding would be exacerbated [26]. Taken together, the use of anticoagulants cannot be thoroughly recommended in cirrhotic patients with non-tumoral PVT.

The theoretical benefits of TIPS for non-tumoral PVT in the setting of liver cirrhosis lie in not only resolving cirrhotic portal hypertension by creation of a portocaval shunt, but also recanalizing the thrombosed portal vein by endovascular manipulations [27]. Indeed, several large case series have confirmed the feasibility, safety and efficacy of TIPS for the treatment of non-tumoral PVT in liver cirrhosis [24,28–31]. The rate of technical success is high (75–100%) (Table 1). Once TIPS is successfully inserted, 87–100% of PVT patients can achieve portal vein recanalization. It is important to note that the degree of PVT is more severe (>50% of lumen occupancy or complete occlusion) in patients undergoing TIPS than those receiving anticoagulation, but TIPS insertion is not recommended in patients with obliterated main portal vein or fibrotic cord if there was no large collateral vessel [32]. Additionally, there is risk of TIPS procedure-related complications, especially intraperitoneal hemorrhage caused by laceration of the portal vein or liver capsule. However, the rate of procedure-related complications is very low (0–15%) (Table 1). In these studies, all but 1 patient, who died of intra-abdominal hemorrhage secondary to hepatic capsule perforation, were cured. The rate of shunt dysfunction and hepatic encephalopathy after TIPS insertion is similar between patients with and without PVT (shunt dysfunction: 28% *vs.* 35%; 2-year hepatic encephalopathy: 27% *vs.* 29%) [31].

Current Recommendations for the Prevention of Variceal Rebleeding in Cirrhosis

As far as cirrhotic patients without PVT are concerned, Baveno V consensus and AASLD practice guidelines regarding the secondary prophylaxis of variceal bleeding have clearly recommended that combination of non-selective beta-blockers (NSBB) and endoscopic therapy is the preferred therapy, as it results in lower rate of variceal rebleeding compared to either therapy alone [16,33]. Contrarily, TIPS insertion is regarded as just a second-line therapeutic option for the patients who fail pharmacological plus endoscopic treatment for the prevention of variceal rebleeding. The recommendation is primarily because TIPS increases the risk of hepatic encephalopathy without any beneficial effect on survival, although it can effectively prevent variceal rebleeding [34,35], but it is uncertain whether the treatment strategy in cirrhotic patients without PVT can be extrapolated to those with non-tumoral PVT.

The beneficial effects of NSSB on cirrhotic portal hypertension are the reduction of portal pressure, which originates from the blockage of β1 receptor that reduces the cardiac output, and the blockage of β2 receptor that reduces portal blood inflow through splanchnic vasoconstriction [36], but the reduced portal flow is the most important predictor for the development of PVT in cirrhotic patients [7]. Thus, NSSB may aggravate the degree and extension of thrombus on the cirrhotic patients with pre-existing PVT. On the

Table 1. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis in liver cirrhosis: A brief review of the literature.

Authors	Luca et al.	Han et al.	Perarnau et al. #	Van Ha et al.	Blum et al.
Journal (published year)	Gut (2011)	J Hepatol (2011)	EJGH (2010)	CVIR (2006)	Radiology (1995)
Number of patients (n)	70	57	34	15	7
Period of enrollment	2003.1-2010.2	2001.12-2008.9	1990-2004	1995.12-2003.12	1990.1-1994.3
Age (years)	Mean±SE: 55±8	Mean±SE: 51±1.6	Mean±SE: 55±11	Range: 45-75	Range: 39-61
Sex (F/M)	23/47	20/37	16/18	2/13	3/4
Indications (n)	RVB (48); Refractory ascites or hydrothorax (18); PVT alone (4)	RVB (56); Refractory ascites (1)	AVB (13); RVB (14); Refractory ascites (5); Others (2)	RVB (10); Refractory ascites or hydrothorax (5)	AVB (2); RVB (5)
Child-Pugh A/B/C (n)	17/42/11	25/26/6	3/11/7 *	0/11/4	0/2/5
Extension of PVT (n)	MPV (67); SMV (55); SV (18)	MPV (57); SMV (43); SV (45)	N/A	MPV (15); SMV (2)	MPV (7); SMV (2); SV (2)
Degree of PVT (n)	Stenosis<50% (31); Stenosis>50% (39)	Partial (stenosis>50%) (35); Complete (14); Fibrotic cord (8)	Complete (34)	Partial (stenosis>50%) (9); Complete (4)	Complete (7)
CTPV (n)	2	30	19	4	0
TIPS insertion success rate (%)	100%	75%	79%	87%	100%
Approaches	Transjugular	Transjugular; Transhepatic; Transsplenic	Transjugular	Transjugular; Transhepatic	Transjugular
PSG (Pre-TIPS / Post-TIPS)	Mean±SE: 20.8±5.8 / 8.5±4.1 mmHg	Mean±SE: 25.7±1.1 / 14.0±0.9 mmHg	Mean±SE: 20.3±5.5 / 7.9±3.8 mmHg	Mean (range): 20 (16–33) / 8 (6–10) mmHg	Mean±SD: 25.5±6.3 / 13.6±3.8 cmH_2O
Procedural complications (n)	1	3	5	1	0
Shunt dysfunction rate (%)	1-, 2-year cumulative rate: 38%, 85% for bare stents; 21%, 29% for covered stents	1-, 2-year cumulative rate: 21%, 32% for bare stents	Long-term stent stenosis: 28%	Long-term stent stenosis: 40%	Long-term stent stenosis: 14%
Prognosis (%)	1-, 2- year cumulative survival rate: 89%, 81%	**TIPS success:** 1-, 5- year cumulative survival rate: 86%, 77%; **TIPS failure:** 1-, 5- year cumulative survival rate: 78%, 62%	1-, 2-, 4-year cumulative survival rate: 80%, 72%, 55%	**TIPS success:** mortality: 31% (4/13) **TIPS failure:** mortality: 50% (1/2)	Mortality: 14% (1/7)

– the patients with partial PVT were excluded from this study; * – 21 of 34 patients had been evaluated for Child-Pugh classification.
AVB – acute variceal bleeding; CTPV – cavernous transformation of the portal vein; MPV – main portal vein; N/A – not available; PSG – portosystemic pressure gradient; PVT – portal vein thrombosis; RVB – recurrent variceal bleeding; SD – standard deviation; SE – standard error; SMV – superior mesenteric vein; SV – splenic vein; TIPS – transjugular intrahepatic portosystemic shunt.

other hand, portal pressure is elevated in 68–72% of cirrhotic patients with a history of variceal bleeding after variceal obliteration by endoscopic band ligation or sclerotherapy [37,38]. In parallel, the presence of extrahepatic portal vein obstruction may magnify the above-mentioned deleterious effect by increasing extrahepatic vascular resistance. Thus, portal pressure elevation may potentially increase the incidence of variceal rebleeding and the number of treatment sessions required to achieve variceal obliteration [38]. By comparison, successful TIPS insertions can significantly reduce the portosystemic pressure gradient in these patients [24,30]. The incidence of variceal rebleeding is significantly lower in patients with successful TIPS insertions than those without (the 1- and 5-year cumulative variceal rebleeding rates are 10% and 28% *vs.* 43% and 100%, respectively) [24]. The short-term survival in patients with successful TIPS insertions is excellent (the 1- and 2-year cumulative survival rates are 80–89% and 72–81%) [24,30], and the long-term

prognosis in these patients appears to be higher than that in general patients with decompensated cirrhosis (the median survival time is 2 years [39]).

With the use of polytetrafluoroethylene-covered stents, the role of TIPS in the management of portal hypertension is progressing [40]. A meta-analysis has recently demonstrated that the covered stents can improve shunt patency, with a trend towards better survival [41]. More recently, a multi-center randomized controlled trial has shown that early use of TIPS with covered stents is associated with significant reductions in treatment failure and mortality, compared with conventional therapy for the treatment of acute variceal bleeding (i.e., vasoactive drugs, prophylactic antibiotics and endoscopic techniques) [42,43]. This important finding strongly suggests that TIPS with covered stents may be regarded as the first-line treatment for acute variceal bleeding in cirrhotic patient with Child-Pugh class B or C. Another multi-center randomized controlled trial is ongoing (ClinicalTrials.gov number, NCT00570973), which aims at comparing the efficacy of TIPS with covered stents and conservative therapy for the prevention of variceal rebleeding in cirrhosis without PVT. Collectively, it is worthwhile to evaluate whether or not TIPS with covered stents is superior to conservative therapy for management of variceal bleeding in cirrhotic patients with non-tumoral PVT (ClinicalTrials.gov number, NCT01326949).

HYPOTHESIS

Evidence and theoretical benefits of TIPS indicate that: 1. it may achieve portal vein recanalization more frequently and safely than anticoagulation therapy, especially in cirrhotic patients with occlusive PVT and a history of variceal bleeding; and 2. the rate of variceal rebleeding is significantly lower in patients undergoing TIPS than that in those receiving endoscopic therapy combined with NSSB. Thus, we further hypothesize that TIPS may be superior to conservative therapy for the prevention of variceal rebleeding in cirrhotic patients with non-tumoral PVT. Certainly, the survival benefit of TIPS should be actively validated in randomized controlled trials.

Conflicts of interest statement

None declared.

Abbreviations

AASLD – American Association for the Study of Liver Diseases; **CTPV –** cavernous transformation of the portal vein; **NSBB –** non-selective beta-blockers; **PVT –** portal vein thrombosis; **TIPS –** transjugular intrahepatic portosystemic shunt.

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