Int J Clin Exp Med 2015;8(10):19709-19716
www.ijcem.com /ISSN:1940-5901/IJCEM0014016

Original Article

Hepatic venous pressure gradient is a useful predictor in guiding treatment on prevention of variceal rebleeding in cirrhosis

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Received August 5, 2015; Accepted October 10, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Background: The best therapy to prevent esophageal variceal (EV) rebleeding in cirrhotic patients who are non-responsive to pharmacological therapy have not been determined. Aims: To evaluate efficacy of a strategy to assign different treatments according to hepatic vein pressure gradient (HVPG) values to prevent EV rebleeding in non-responders. Methods: This study is a non-randomized controlled prospective study. 109 cirrhotic patients with EV bleeding who were non-responders based on two HVPG measurements were enrolled and divided two groups: 55 patients (EVL+β-blocker group) were treated with endoscopic variceal ligation (EVL) and nonselective β-blocker; 54 patients (HVPG-guided group) were treated with EVL and nonselective β-blocker if HVPG ≤ 16 mmHg (low-HVPG), with percutaneous transhepatic variceal embolization (PTVE) if HVPG > 16 mmHg and ≤ 20 mmHg (medium-HVPG), or with transjugular intrahepatic portosystemic shunt (TIPS) if HVPG > 20 mmHg (high-HVPG). Patients were followed up for rebleeding and mortality. Results: The mean follow-up period was 17.0 months; rebleeding was higher in the EVL+β-blocker group than HVPG-guided group (25.5%, 9.3%, P = 0.026); 3-year probability of rebleeding in the EVL+Beta-blocker group increased with elevated levels of HVPG (12.5% vs 46.4% vs 64.9%, χ^2 = 11.551, P = 0.003), and 3-year probability of survival was no difference (96.6% vs 85.7% vs 90.9%, χ^2 = 2.638, P = 0.267). Rebleeding rate in PTVE group (7.7%) was lower than that in EVL+β-blockergroup with medium-HVPG (35.7%), but there was no difference. Rebleeding rate in TIPS group (7.7%) was lower than that in EVL+β-blockergroup with high-HVPG (45.5%), but there was no difference. Conclusions: HVPG measurement was useful for making decisions to select EVL and Beta-blocker, PTVE or TIPS in secondary prophylaxis. HVPG-guided treatment is feasible and effective in preventing esophageal varices rebleeding.

Keywords: Esophageal varices bleeding, endoscopic variceal ligation, percutaneous transhepatic variceal embolization, transjugular intrahepatic portosystemic shunt, hepatic vein pressure gradient

Introduction

A combination of beta-blockers and band ligation is the preferred therapy for patients with cirrhosis to prevent rebleeding, and the hemodynamic response to drug therapy provides information about rebleeding risk and survival [1-3]. The lowest rate of variceal rebleeding (≈ 10%) is obtained in patients who are HVPG responders (HVPG ≤ 12 mm Hg or ≥ 20% decrease from baseline) [3]; however, hemodynamic responses to β-blockers occur in only approximately one third of patient [4], and approximately 50% of patients with viral cirrhosis lose the hemodynamic response in 2 years and show a higher incidence of death or liver transplantation [5, 6]. The rebleeding rate in non-responders is as high as 46% [7], and one study has shown that adding EVL to pharmacological treatment did not reduce recurrent bleeding or mortality, and it was associated with more adverse events for non-responders [8]. Thus, the best therapies for non-responders have not been determined.

As suggested recently, perhaps the most rational therapy would be to adapt the different therapies to prevent variceal rebleeding in the con-

text of HVPG measurement [9]. In this study, the different therapeutic options were assigned according to the level of HVPG values in non-respond patients; the aim of the study was to value the effect of treatment strategy in preventing variceal rebleeding in hemodynamic non-responders.

Methods

Patient selection and study protocol

123 cirrhotic patients with acute variceal bleeding were initially considered for the study between September 2010 and December 2013. 9 patients were excluded because of the following criteria, 3 patients were excluded because of postoperative lost, 2 patients were excluded because of non-responders, and ultimately effective cases was 109 patients. Patients and their families divided into the group after signing informed consent.

The inclusion criteria: (1) Esophageal variceal bleeding by emergency endoscopic; (2) Clinical manifestations, laboratory tests and liver biopsy or imaging studies confirmed cirrhosis; (3) Patients and their families agreed to the preoperative and postoperative review project; (4) Patients were responder on β-blocker.

The exclusion criteria: (1) age greater than 75 years; (2) failure to control acute variceal bleeding; (3) with β-blocker use history or endoscopic varicose vein treatment history; (4) advanced liver cancer; (5) portal vein thrombosis; (6) Child-Pugh classification standard score > 12 points; (7) contraindications to beta-blocker; (8) HVPG < 10 mmHg; (9) severe coronary heart disease, hypertension, heart, and lung failure.

A full clinical history was obtained, and physical examination, laboratory tests, electrocardiography, chest radiography, and ultrasonography were performed. All patients with acute bleeding were treated with an infusion of vasoactive drugs (somatostatin or terlipressin) for 3-5 days and received oral norfloxacin (400 mg BID) or intravenous ciprofloxacin (1 g QD) prophylaxis for 7 days. To detail records of the patient 's age, sex, cause of cirrhosis, ascites grading, grading of hepatic encephalopathy , aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum total bilirubin (TBIL), albumin (ALB), platelet count (PLT), hemoglobin (HGB), white blood cell count (WBC), prothrombin time (PT), international normalized ratio (INR). Child-Pugh classification applied to patients with hepatic functional reserve quantitative assessment.

Endoscopy was performed within 48 hours for all patients to make the diagnosis and to treat variceal hemorrhage with EVL. A baseline hemodynamic study was performed according to recommended standards 2-3 days after cessation of bleeding 10. Vasoactive drugs were stopped for at least 24 h before HVPG measurement. According HVPG measurements, patients were divided into three levels HVPG: (1) low-HVPG: 10 mmHg ≤ HVPG ≤ 16 mmHg; (2) medium-HVPG: 16 mmHg < HVPG ≤ 20 mmHg; (3) high-HVPG: HVPG > 20 mmHg. The treatment choice was based on the clinical judgment and patient choice. The treatment choice was based on the clinical judgment and patient choice. In clinic, PTVE would be preferentially chosen in patients with previous HE, while TIPS would be preferentially used in patients with massive ascites or portal thrombosis. The choice of treatment was left to the patient after sufficient explanation of the procedure, methods, principle, and the possible complications of EVL, PTVE and TIPS in details. We only maintained responders on β-blocker. 55 patients agreed to accept EVL+β-blocker treatment, and we named them as EVL+β-blocker group. These include low-HVPG 30 patients, medium-HVPG 14 patients and high-HVPG 11 patients. 54 patients agreed to choose treatment options according HVPG measurements, and we named them HVPG-guided group. 28 low-HVPG patients accepted EVL+β-blocker treatment; 13 medium-HVPG patients accepted PTVE, and 11 high-HVPG patients accepted TIPS.

Treatments

Endoscopic variceal ligation: Ligation was performed using commercial multiband devices (Wilson-COOK Medical Inc, North Carolina, USA). The procedure was performed under conscious sedation with propofol (AstraZeneca S.p.A, Italy) and continuous monitoring of pulse rate, oxygen saturation and arterial pressure. To learn varicose veins range, extent, determine the ligation site under the endoscopic. Ligation direction from the cardia to the oral side. Ligation was performed at 4-week intervals until variceal eradication had been achieved. The varices were considered to have been eradicated when they had either disap-

Table 1. The clinical and laboratory characteristics of the patients enrolled in the study

Characteristics	EVL+β-blocker group (N = 55)	HVPG-guided group (N = 54)	*P*-value
Gender			0.621
Male, number (%)	42 (76.4%)	39 (72.2%)	
Female, number (%)	13 (23.6%)	15 (27.8%)	
Age, years			0.581
Mean ± s.d.	53.3±11.3	50.9±10.7	
Etiology			0.148
Viral, number (%)	28 (50.9%)	35 (64.8%)	
Alcohol, number (%)	9 (16.4%)	10 (18.5%)	
Others, number (%)	18 (32.7%)	9 (13.4%)	
Child-Pugh class			0.683
A, number (%)	22 (40.0%)	26 (48.1%)	
B, number (%)	29 (52.7%)	25 (46.3%)	
C, number (%)	4 (7.3%)	3 (5.6%)	
Esophageal varices#			0.263
Small, number (%)	0 (0.0%)	2 (3.7%)	
Medium, number (%)	4 (7.3%)	2 (3.7%)	
Large, number (%)	51 (92.7%)	50 (92.6%)	
Gastric varices			0.113
Yes, number (%)	54 (98.2%)	49 (90.7%)	
No, number (%)	1 (1.8%)	5 (9.3%)	
Ascites			0.322
Yes, number (%)	32 (58.2%)	37 (68.5%)	
No, number (%)	23 (41.8%)	17 (31.5%)	
ALT (IU/L)			
Mean ± s.d.	31.7±18.6	37.4±24.7	0.107
AST (IU/L)			
Mean ± s.d.	41.1±22.7	45.5±25.2	0.207
Albumin (g/L)			
Mean ± s.d.	32.9±5.6	34.3±5.1	0.303
Bilirubin (μmol/L)			
Mean ± s.d.	23.0±12.8	26.3±22.7	0.281
Prothrombin time (s)			
Mean ± s.d.	15.1±2.5	14.9±2.1	0.137
Hb (g/dL)			
Mean ± s.d.	91.9±26.2	90.5±23.1	0.375
WBC, $\times 10^{12}$/L			
Mean ± s.d.	4.4±2.6	3.6±1.9	0.246
Platelets, $\times 10^{9}$/L			
Mean ± s.d.	120.5±103.4	97.4±71.4	0.056
HVPG (mmHg)			
Mean ± s.d.	16.0±5.5	17.0±5.8	0.375
Low-HVPG, number (%)	30 (54.5%)	28 (51.9%)	
Medium-HVPG, number (%)	14 (25.5%)	13 (24.1%)	
High-HVPG, number (%)	11 (20.0%)	13 (24.1%)	

peared or could not be grasped and banded using the ligator.

β-blockers: Patients take propranolol (10 mg tid), monitoring of blood pressure, heart rate, and gradually increase the dose of propranolol, up to 25% reduction of heart rate or below 55 beats/min.

Modified PTVE procedure: The PTVE procedure was performed under radiological guidance as described previously [10]. In brief, after transhepatic puncture of the intrahepatic portal vein branch, splenoportography was performed to evaluate the index varices as well as the feeding vessels and draining veins. The main feeding vessels, including the left, short, and posterior gastric veins, were selected and 2-octyl cyanoacrylate (Guangzhou Baiyun Medical Adhesive Corporation, Guangzhou, China) was injected; splenoportography was repeated subsequently to assess the extent of the obliteration of the varices. If other feeding vessels were detected, the procedure was repeated until blood flow in the varices ceased completely. Finally, the lower EVs and peri-EVs and/or the gastric cardiac submucosal and perforating vessels were obliterated with 2-octyl cyanoacrylate.

Transjugular intrahepatic portosystemic shunt: The TIPS procedure was carried out as described by Funaki [11]. The patients received uncoated prostheses (Wallstent, Boston Scientific, Natick, MA, USA) and the HVPG was reduced to < 12 mmHg. After the procedure, at 7 days, 1, 3 and 6 months and 1 year following TIPS implantation, Doppler ultrasonography was performed to investigate the shunt. Following this, Doppler ultrasound examination of the liver was performed at 6-month intervals. When rebleeding occurred or ultrasound examination revealed shunt dys-

ALT, alanine aminotransferase; AST, aspartate transaminase; Hb, hemoglobin; WBC, white blood cells; EVL, endoscopic variceal ligation; HVPG, hepatic vein pressure gradient. #Small varices: minimally elevated veins above the esophageal mucosal surface; Medium varices: tortuous veins occupying less than one-third of the esophageal lumen; Large varices: tortuous veins occupying more than one-third of the esophageal lumen. *Low-HVPG: 10 mmHg < HVPG ≤ 16 mmHg; Medium-HVPG: HVPG > 16 mmHg and ≤ 20 mmHg; High-HVPG: HVPG > 20 mmHg.

Table 2. Rebleeding and mortality of patients in the EVL+β-blocker group and HVPG-guided group during follow-up

	EVL+β-blocker group (N = 55)	HVPG-guided group (N = 54)
Overall rebleeding	14	5
From varices	12	5
From portal hypertensive gastropathy	1	0
From EVL-related ulcers	1	0
Overall mortality	4	3
Bleeding-related	4	2

EVL, endoscopic variceal ligation; HVPG, hepatic vein pressure gradient.

function, angiography was performed and intervention was applied with the use of balloon dilation and implantation of a bare metal stent to support the narrow shunt.

Follow-up: The main endpoint of the study was recurrent bleeding from any source; the secondary endpoint was mortality. All patients were followed up at 3-month intervals until rebleeding, death or the end of the study, and were instructed to come to the hospital if they experienced melena or hematemesis. If bleeding was confirmed, an emergency endoscopy was performed. Variceal bleeding was diagnosed when varices were bleeding actively or showed stigmata of recent bleeding, and/or if fresh blood was observed in the stomach and varices were the only potential source of bleeding. Bleeding was considered to be related to the EVL when endoscopy showed that bleeding had occurred from an ulcer that had developed secondary to previous ligation. In both groups, the rebleeding episodes were treated with vasoactive drugs (somatostatin or terlipressin) and/or emergency sclerotherapy, EVL or TIPS.

Statistical analysis

All data were expressed as the mean ± standard deviation. Frequency variables were compared using the Pearson's chi-squared test, or Fisher's exact test when necessary. Quantitative variables were analyzed using the Student's *t*-test, or one-way analysis of variance (ANOVA). The cumulative risks of rebleeding and mortality were evaluated by the Kaplan-Meier method. Comparisons between different groups were made with the log-rank test. The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 19.0 was used, and $P < 0.05$ was regarded as significant.

Results

The basic clinical characteristics, laboratory features, hemodynamic characteristics of 109 patients of liver cirrhosis were as follows in **Table 1**. The etiologies of the liver cirrhosis included viral hepatitis, alcoholic liver disease, and other causes, in 63 (57.8%), 19 (17.4%) and 27 (24.8%) respectively. Child-Pugh's class A, B, and C of liver cirrhosis was established in 48 (44%), 54 (49.5%), 7 (6.5%) patients, respectively. Most patients with esophageal varices (severe), accompanied with gastric varices. Low-HVPG, medium-HVPG, and high-HVPG was 58 patients, 27 patients, and 24 patients, respectively.

Rebleeding and mortality during follow-up in the HVPG-guided group and the EVL+β-blocker group

The 109 patients included in the study were followed up for a mean of 17.0 months (range 0.5 months-40 months). There was no difference in the follow-up time (16.4 vs 17.7 months, t = -0.627, $P = 0.532$) and the distribution of HVPG values between the EVL+β-blockergroup and the HVPG-guided group ($\chi^2 = 0.264$, $P = 0.877$). No differences in clinical and laboratory characteristics were observed between the two groups (**Table 1**).

Table 2 summarizes the rebleeding and mortality in the two groups during the follow-up period. A total of 19 patients, 14 in the EVL+β-blocker group and 5 in the HVPG-guided group, rebleeding during follow-up; the incidence of rebleeding in the EVL+β-blockergroup was 25.5% (14/55), whereas it was only 9.3% (5/54) in the HVPG-guided group ($\chi^2 = 4.966$, P = 0.026). There was a significant difference in the 3-year cumulative rebleeding (26.2% vs. 25.0%, $P = 0.049$). Kaplan-Meier curves for rebleeding are shown in **Figure 1**. A total of 7 patients died

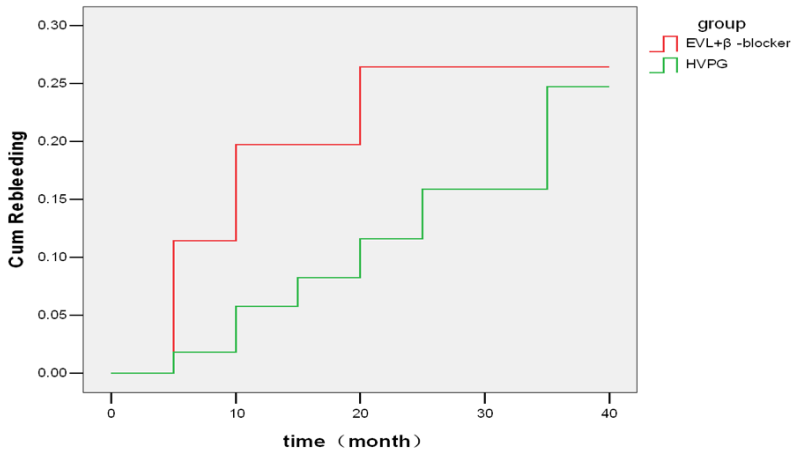

Figure 1. Kaplan-Meier curves for rebleeding.

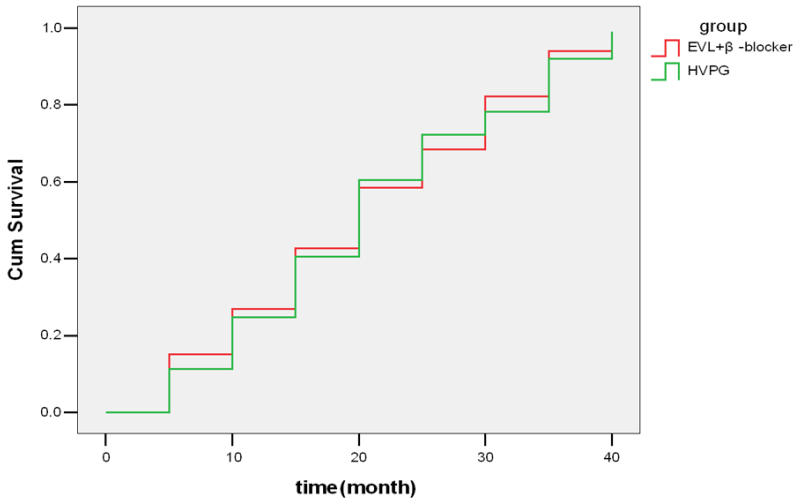

Figure 2. Kaplan-Meier curves for survival.

during the follow-up period, 4 patients in the EVL+β-blocker group and 3 patients in the HVPG-guided group. The causes of death were hepatorenal syndrome (one patient), variceal bleeding (six patients). Mortality was not different between the two groups (χ^2 = 0.134, P = 0.715). There was no significant difference in the 3-year cumulative survival (98.0% vs. 98.8%, P = 0.767). Kaplan-Meier curves for survival are shown in **Figure 2**.

Varicesrebleeding and mortality in the EVL+β-blocker-treated patients with different HVPG values

83 patients who accepted EVL+β-blocker treatment were divided into 3 groups according to HVPG values: 58 patients were in the low-HVPG group, including 30 patients in the EVL+β-blocker group and 28 patients in the HVPG-guided group; 14 patients were in the medium-HVPG group; and 11 patients were in the high-HVPG group. There was no difference of data in clinical and laboratory characteristics among the three groups (**Table 3**).

Rebleeding rate was 35.7% in the medium-HVPG group, and it was 12.1% in the low-HVPG group. There was significant difference of rebleeding rate between the low-HVPG group and medium-HVPG group (χ^2 = 4.540, *P* = 0.033). Rebleeding rate was 45.5% in the high-HVPG group, and there was significant difference of rebleeding rate between the low-HVPG group and high-HVPG group (χ^2 = 7.174, *P* = 0.007). With the increase in HVPG, the rebleeding rate had a rising trend in patients with EVL+β-blocker treatment.

Mortality was 14.3% in medium-HVPG group, and it was 3.4% in low-HVPG group. There was no difference of mortality between medium-HVPG group and low-HVPG group (χ^2 = 2.524, *P* = 0.112). Mortality was 9.1% in high-HVPG group, and there was no difference between high-HVPG group and low-HVPG group (χ^2 = 0.708, P = 0.4).

Differences in rebleeding and mortality between the medium-HVPG group with EVL+β-blocker-treated and the PTVE-treated group

There was no difference of data in clinical and laboratory characteristics between medium-HVPG group with EVL+β-blocker treated and PTVE-treated group. Rebleeding rate was 35.7% in medium-HVPG group with EVL+β-

Table 3. Rebleeding and mortality in the EVL+β-blocker-treated patients with different HVPG values

	Low-HVPG group (N = 58)	Medium-HVPG group (N = 14)	High-HVPG group (N = 11)
Rebleeding Number (%)	7 (12.6%)	5 (35.7%)*	5 (45.5%)**
Mortality Number (%)	2(3.45%)	2 (14.3%)	1 (9.1%)

EVL, endoscopic variceal ligation; HVPG, hepatic vein pressure gradient. Low-HVPG group: 10 mmHg < HVPG ≤ 16 mmHg; Medium-HVPG group: HVPG > 16 mmHg and ≤ 20 mmHg; High-HVPG group: HVPG > 20 mmHg. *P = 0.033 (low-HVPG group vs. medium-HVPG group). **P = 0.007 (low-HVPG group vs. high-HVPG group).

Table 4. Rebleeding and mortality between the EVL+β-blocker-treated group and PTVE-treated group in patients with medium-HVPG

	EVL+β-blocker-treated group (N = 14)	PTVE-treated group (N = 13)	*P*-value
Rebleeding Number (%)	5 (35.7%)	1 (7.7%)	0.165
Mortality Number (%)	2 (14.3%)	1 (7.7%)	1.000

EVL, endoscopic variceal ligation; PTVE, percutaneous transhepatic variceal embolization; HVPG, hepatic vein pressure gradient.

Table 5. Rebleeding and mortality between the EVL+β-blocker-treated group and TIPS-treated group in patients with high-HVPG

	EVL+β-blocker-treated group (N = 14)	TIPS-treated group (N = 13)	*P*-value
Rebleeding Number (%)	5 (45.5%)	1 (7.7%)	0.165
Mortality Number (%)	1 (7.1%)	1 (7.7%)	1.000

EVL, endoscopic variceal ligation; TIPS, Transjugular intrahepatic portosystemics-hunt; HVPG, hepatic vein pressure gradient.

blocker treated,and it was 7.7% in PTVE-treated group. But there was no difference in both group (P = 0.165). Mortality was 14.3% in medium-HVPG group with EVL+β-blocker treated, and it was 7.7% in PTVE-treated group. There was also no significant difference in mortality between the two groups (P = 1.000) (**Table 4**).

Differences in rebleeding and mortality between the high-HVPG group with EVL+β-blocker-treated and the PTVE-treated group

There was no difference of datas in clinical and laboratory characteristics between high-HVPG group with EVL+β-blocker treated and TIPS-treated group. Rebleeding rate was 45.5% in high-HVPG group with EVL+β-blocker treated, and it was 7.7% in TIPS-treated group (P = 0.061). Mortality was 7.1% in high-HVPG group with EVL+β-blocker treated, and it was 7.7% in TIPS-treated group. There was also no significant difference in mortality between the two groups (P = 1.000) (**Table 5**).

Adverse effects

20 patients had a transient chest pain and 6 patients had a fever in EVL+β-blocker-treated group. 3 patients had a transient abdominal pain and 2 patients had a fever and 1 patient had a bleeding puncture site in PTVE-treated group. 6 patients had hepatic encephalopathy during follow-up.

Discussion

The results of our study indicate that the strategy of assigning treatment according to HVPG values is feasible and effective in protecting patients from variceal rebleeding. Some studies seemed to indicate that the rebleeding risk varied according to the HVPG value [12-14]. The level of portal pressure holds information on prognosis, risk of bleeding and rebleeding from esophageal varices [15, 16].

Our study presented an impressive 9.3% rebleeding rate in the HVPG-guided group (compared with 25.5% in the EVL+β-blocker group), which indicates the high efficacy of the strategy utilized. Patients with higher HVPG levels have an increased probability of rebleeding; PTVE and TIPS are superior to EVL combine with β-blocker for treatment of these patients.

Until now, there have been few studies on the relationship between the outcomes of EVL and different HVPG values. In this study, we divided patients into different groups on HVPG values. We found that patients with high-HVPG (HVPG > 20 mmHg) had a higher rate of recurrence of varices than patients with low-HVPG (HVPG ≤ 16 mmHg) in EVL+β-blocker group. Accordingly, rebleeding was increased in patients with high-HVPG compared with patients with low-HVPG, while mortality was no significant differencein different HVPG values.

Our study indicated that the HVPG value is a factor in predicting the outcome of EVL combine with β-blocker: in patients with a high HVPG value, EVL combine with β-blocker per-

haps is not an appreciate choice for the prevention of variceal rebleeding.

Our study showed that PTVE is an important choice for prevention of variceal rebleeding in cirrhosis patients. Through extensive and long-term blood vessels embolism, PTVE could decrease variceal rebleeding. In this study, we found that variceal rebleeding in PTVE group was lower than that in medium-HVPG group with EVL combine with β-blocker (7.7% vs 35.7%, $P = 0.165$). This indicates PTVE may be a favorable alternativeto medium-HVPG patients.

TIPS is recommended as a rescue therapy after failure of combined medical and endoscopic therapy for the prevention of variceal hemorrhage in current guidelines [1, 3]. Although the long-term patency rate was improved because of the use of the coated stent, a higher encephalopathy rate and cost in the TIPS group still limit its clinical application [17, 18]. In this study, we found that variceal rebleeding in TIPS group was lower than that in high-HVPG group with EVL combine with β-blocker (7.7% vs 45.5%, $P = 1.000$). This result indicates TIPS may be a favorable alternative to high-HVPG patients.

While in a recent study, we compared the long-term results of PTVE and TIPS for the treatment of esophageal varices in terms of rebleeding rate, survival and the rate of encephalopathy [19]. The result indicates that the modified PTVE was similar with TIPS for the prevention of variceal rebleeding, but the encephalopathy incidence is remarkable lower in PTVE group than TIPS group. According to these studies, we proposed that PTVE may be perfect for these patients with a medium HVPG than TIPS.

Although the number of treated patients was small, our study indicated that the measurement of HVPG is useful when making a decision to select EVL combine with β-blocker, PTVE or TIPS in secondary prophylaxis.

There are some limitations to our study. This was a pilot study in one hospital, with the limits of observations made outside the setting of a randomized controlled trial. In addition, the sample size is small; although the groups appear demographically similar there may have been bias introduced as the assignment was not randomized; therefore, further studies will be needed in larger groups of patients and multiple research centers to confirm the results.

In conclusion, patients with high HVPG values have a high risk of rebleeding despite EVL combine with β-blocker. In patients with medium or high HVPG values, PTVE or TIPS may be a favorable alternative to EVL combine with β-blocker.

Disclosure of conflict of interest

None.

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