Effect of Propranolol on Portal Pressure and Systemic Hemodynamics in Patients with Liver Cirrhosis and Portal Hypertension: A Prospective Study

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Background/Aims: Propranolol can prevent variceal bleeding by ameliorating portal hypertension. We conducted this study to determine the effect of propranolol on portal hypertension and the optimal required dose in Korean cirrhotic patients. **Methods:** This study prospectively evaluated 50 patients with cirrhosis who exhibited variceal bleeding. The hepatic venous pressure gradient (HVPG), portal venous flow, heart rate (HR), and blood pressure were assessed both at baseline and at 3 months after the treatment. The initial dose of propranolol (20 mg) was subsequently adjusted until the target HR was reached. Patients in whom HVPG reduced by $>20\%$ or to less than 12 mmHg were defined as responders. **Results:** Propranolol significantly ($p<0.01$) reduced the HVPG ($-21\pm 26\%$, mean $\pm$ standard deviation), portal venous flow ($-25\pm 21\%$), HR ($-20\pm 13\%$), and blood pressure ($-3\pm 13\%$). Twenty-nine patients were responders, and the optimal required dose was 154.4 mg. The main complication was dizziness (24%), but this was not serious enough to require medication withdrawal. **Conclusions:** Propranolol is safe and effective at reducing portal pressure in Korean cirrhotic patients. An effective improvement in portal hypertension requires the dose to be increased until the target HR is reached. (*Gut and Liver* 2007;1:159-164)

Key Words: Propranolol; Portal hypertension; Liver cirrhosis; Pressure

INTRODUCTION

Variceal hemorrhage is a common and severe complication of portal hypertension in patients with cirrhosis. Up to 30% of initial bleeding episodes are fatal and as many as 70% of survivors have recurrent bleeding within one year.¹ The options currently available for treatment of the variceal bleeding are pharmacotherapy, endoscopic variceal ligation, endoscopic sclerotherapy, transjugular intrahepatic portosystemic shunt, and surgical portocaval shunt.^{2,3} Among these treatments, pharmacotherapy has been used to correct the increased portal blood flow and pressure.⁴⁻⁸

Propranolol, a nonselective β blocker, has been shown to be effective for the prevention of variceal bleeding and rebleeding, and is widely used as the pharmacotherapy for the treatment of portal hypertension in patients with cirrhosis.⁹⁻¹¹ It has been shown that reduction of hepatic venous pressure gradient (HVPG) of at least 20% from the baseline levels, preferably below 12 mmHg was associated with marked reduction of the risk of variceal bleeding. However, in the previous studies,^{12,13} there were racial differences in treatment sensitivity to propranolol. Therefore, it is important to determine the effect of propranolol on portal hypertension in Korean patients. We conducted this study to determine the effect of propranolol on portal hypertension and the required optimal dose for Korean patients with cirrhosis.

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Received on July 30, 2007. Accepted on December 10, 2007.

This work was supported by a grant from Ministry of Health and Welfare, Republic of Korea (Grant A050021) and also by a grant from Yonsei University Wonju College of Medicine Research Fund of 2005.

MATERIALS AND METHODS

Fifty patients with cirrhosis who were admitted to the Wonju Christian Hospital of Wonju College of Medicine with acute variceal bleeding from January 2002 to December 2006 were prospectively enrolled in this study. The bleeding was controlled by emergency endoscopy. All patients received either endoscopic variceal ligation or sclerotherapy. The patients with severe hepatic failure, hepatic encephalopathy, hepatoma, history of surgery to portal hypertension, history of use of β blocker medication, or patients with contraindications to β blocker treatment were excluded in this study. A written informed consent was obtained from each patient and the ethics committee of our hospital approved the study protocol.

Liver cirrhosis was clinically diagnosed by physical examination, laboratory findings, ultrasound, and upper gastrointestinal endoscopy. At 2-5 days after the initial emergency endoscopy, we conducted a baseline evaluation including family and alcohol history, X-ray, electrocardiography, blood test, electrolyte, liver function test, and viral marker. Most patients were hemodynamically stable at 5-7 days after the initial endoscopic therapy. At that time, we performed the hemodynamic studies without any medication that might have an effect on the results and then propranolol was given orally. The hemodynamic studies including measurements of HVP, portal venous flow (PVF), heart rate (HR), and mean blood pressure (MBP) were evaluated at both the baseline and at 3 months after the initiation of propranolol treatment. To determine the change of portal pressure after the initiation of proprano-

lol therapy, we measured the HVP by right hepatic vein catheterization. In addition, we evaluated the change of the PVF by Doppler ultrasonography with an ALOKA SSD 5000 (ALOKA Co., LTD., Tokyo, Japan) using a 3.5 MHz curved transducer.

1. Hemodynamic measurements

A 7 French balloon catheter was placed in the right hepatic vein through the right femoral vein puncture for measurement of the free hepatic venous pressure. The wedged hepatic venous pressure was measured by inflation of the balloon catheter at the right hepatic vein (Fig. 1). Then, the HVP was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure.⁴

Portal venous velocity and cross-sectional area of the portal vein were estimated from a subcostal scan at its crossing point with the hepatic artery. When the sample point was adjusted to the center of the portal vein, the portal venous velocity was recorded during a quiet suspended expiration and was averaged over a few seconds. The PVF was determined by the formula; cross section area $\times$ mean velocity $\times$ 60 (Fig. 2).^{14,15}

The heart rate was derived from continuous electrocardiogram monitoring. The MBP was measured non-invasively with an automated sphygmomanometer (Hewlett-Packard M1205A; Palo Alto, CA).

2. Administration of propranolol

After the initial endoscopy and measurement of hemodynamic parameters, propranolol was given orally at an initial dose of 20 mg twice daily. The dose was sub-

Fig. 1. The measurement of HVP by right hepatic vein catheterization. (A) Seven French balloon catheter is placed in the right hepatic vein to measure the free hepatic venous pressure. (B) The wedged hepatic venous pressure is measured by inflating the balloon catheter at the right hepatic vein. HVP is determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure.

sequently adjusted over a period of 2 days until the resting HR was reduced by 25% or was less than 55 beats per minute. After the target HR was reached, the propranolol was administered for 3 months at the adjusted dosage. All of the patients received follow-up examination on BP, HR, and assessment for complications at regular outpatient clinic visits. Patients who showed reduction in the HVPG of more than 20% of the baseline or an absolute value less than 12 mmHg were defined as responders to the propranolol treatment. All the others were classified as non-responders. In evaluating the relating factors in the responders, age, presence of ascite (no vs. yes) and splenomegaly (no vs. yes), esophageal varix (F0-1 vs. F2-3), child-Pugh score, HR, MBP, FHVP, HVPG, and PVF were used as variables.

3. Statistical analysis

Data were expressed as means and standard deviations.

Fig. 2. The measurement of PVF. Doppler ultrasonography shows a portal venous velocity of 10.8 cm/s and PVF of 480 ml/min in a patient with liver cirrhosis and portal hypertension.

A paired *t*-test was used for comparison of vital signs, free hepatic pressure, wedged hepatic pressure, and HVPG in response to propranolol. The difference between responders and non-responders in the effect of propranolol was calculated by an independent *t*-test. Multivariate logistic regression analysis was performed to identify the factors related to the responders. Data were analyzed with statistical software (SPSS, version 13.0, SPSS Inc., Chicago, Illinois, USA). A *p* value < 0.05 was considered significant for all tests.

RESULTS

1. Patient characteristics

The mean age of the patients (male/female=45/5) was 49.0±9.6 years. The causes of liver cirrhosis were alcohol in 29 (58%), hepatitis B virus in 11 (22%), hepatitis B virus+alcohol in 8 (16%), hepatitis C virus in 1 (2%), and cryptogenic in 1 (2%) patient. Fourteen patients had Child-Pugh class A; 26, class B; and 10, class C (Table

Table 1. Baseline Clinical Characteristics

Age (years)	49.0±9.6
Sex (M : F)	45 : 5
Etiology (%)	
HBV	29 (58)
Alcohol	11 (22)
HBV+alcohol	8 (16)
HCV	1 (2)
Cryptogenic	1 (2)
Child-Pugh (%)	
A	14 (28)
B	26 (52)
C	10 (20)

HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2. Clinical Hemodynamic Features of Responders and Non-responders at 3 Months after Propranolol Administration

	Total (n=50)		Responders (n=29)		Non-responders (n=21)	
	Before	After	Before	After	Before	After
HR (beats/min)	75±11	59±9*	76±11	59±10*	73±11	58±8*
MBP (mmHg)	89±13	84±11*	88±14	83±12 [†]	88±11	85±10
WHVP (mmHg)	28±6	26±6*	28±6	24±6 [†]	27±7	28±6
FHVP (mmHg)	11±4	13±6	11±5	14±6 [†]	11±3	12±4
HVPG (mmHg)	17±5	13±5*	17±5	10±3*	16±5	16±3
PVF (ml/min)	801±323	578±254*	835±284	623±207*	752±375	512±304*

Values are expressed as mean±standard deviation: **p*<0.01, [†]*p*<0.05.

HR, heart rate; MBP, mean blood pressure; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; PVF, portal venous pressure.

1). Hepatitis B virus + alcohol meant that hepatitis B virus infection and alcohol were mixed etiologies of cirrhosis.

2. Hemodynamic changes after medication and required dose of propranolol

The baseline BP and HR were 87.8 ± 12.8 mmHg and 74.7 beat/min. Propranolol treatment resulted in significant reduction in HVP (G) $-21.0 \pm 26.2\%$, $p < 0.01$), portal venous flow ($-25.2 \pm 21.3\%$, $p < 0.01$), HR ($-20.4 \pm 12.9\%$, $p < 0.01$), and mean BP ($-3.3 \pm 13.4\%$, $p < 0.01$) (Table 2). After propranolol administration, the number of drug responders and non-responders were 29 (58%) and 21 (42%), respectively. In the responders, all hemodynamic parameters were significantly reduced after propranolol administration. However, in the non-responders, only HR and PVF were reduced after medication. There were no significant relating factors detected for the responders in the multivariate logistic analysis ($p > 0.05$) (Table 3).

The mean required dose of propranolol to reach the target heart rate was 154.4 ± 59.4 mg (range 80-320 mg). The mean required dose of propranolol in the responders and non-responders was 161.4 ± 61.0 mg and 144.8 ± 57.2 mg, respectively ($p > 0.05$). The optimal doses in the alcohol-etiology-group and the others were 161.1 ± 58.4 mg and 133.3 ± 59.9 mg, respectively ($p > 0.05$). The major complication from the propranolol treatment was dizziness due to orthostatic hypotension, occurring in 24% of patients. However, this was not serious enough to discontinue the administration of the drug.

Table 3. Multivariate Analysis of Relating Factors for Responders

Variables	B	Standard error	Significance
Age	-0.032	0.038	0.405
Ascites (no* vs. yes)	1.554	1.043	0.136
Splenomegaly (no* vs. yes)	-1.331	1.212	0.272
Varix (F0-1* vs. F2-3)	0.263	1.397	0.851
Child-Pugh score	-0.066	0.260	0.801
HR	0.006	0.036	0.858
MBP	-0.003	0.032	0.914
FHVP	-0.034	0.093	0.711
HVP	0.070	0.085	0.410
PVF	0.001	0.001	0.374

*reference category.

B, regression coefficient; HR, heart rate; MBP, mean blood pressure; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVP, hepatic venous pressure gradient; PVF, portal venous pressure.

DISCUSSION

It is now generally agreed that an HVP above the threshold of 12 mmHg is associated with complications from portal hypertension. As a result, the hemodynamic response (decrease of HVP to 12 mmHg or less, or a decrease by at least 20% from the baseline values) to β blocker therapy was found to be the main predictor of clinical effectiveness in patients undergoing therapy for the prevention of rebleeding.^{2,7} β blockers reduce the portal pressure by decreasing cardiac output and azygous blood flow and by causing splanchnic vasoconstriction.² In this study, PVF and HVP were significantly reduced by 25.2% and 21%, respectively following propranolol administration. The results of this study confirmed the efficacy of propranolol in reduction of portal hypertension in Korean patients with cirrhosis.

Racial or ethnic differences in sensitivity to propranolol have been documented.^{12,13} Zhou et al¹⁶ suggested that most absorbed propranolol was combined with plasma proteins such as alpha 1-acid glycoprotein: and the proportion of bound propranolol affects the patient sensitivity. The reason for the interracial difference in the alpha 1-acid glycoprotein level is unknown. Moreover, the precise mechanisms causing differences in sensitivity of β blockade are unclear. In the previous reports,^{5,6,10,11} the responders were 35-45% in Spain and 45-67% in India. Also, propranolol produced a much greater degree of systemic hemodynamic response in people of Chinese as compared with Caucasians.¹⁶ Our findings showed that 29 patients (58%) were responders. In other words, approximately 40% of patients receiving the propranolol are exposed to unnecessary administration of propranolol. Therefore, the development of alternative drug is required for the management of portal hypertension.

Currently, relating factors for responsiveness of propranolol were not unknown in patients with cirrhosis. A previous report has found that old age and prior history of bleeding negatively influences the effect of propranolol.¹¹ However, our data showed no significant distinguishing factors between responders and non-responders. A multi-center study with larger number of subjects might be needed to find out factors related to responders in Korea.

The mean required dose of propranolol to reach the target heart rate was 154.4 mg in this study. This dose of propranolol is somewhat higher than that of expected. However, it can be speculated that patients with portal hypertension could have been treated with suboptimal dose of propranolol, thus be insufficiently managed. Our finding suggests that the dose of propranolol should be sufficiently increased until the target HR is reached. The

most common etiology of cirrhosis in this study was alcohol abuse. Alcohol induces the microsomal enzymes that are involved in the process of "first pass metabolism" of propranolol. Therefore, it can be contemplated that the optimal dose of propranolol might be higher in patients with an alcohol etiology than in those with viral etiology. However, in our results, there was no significant difference in the optimal dose of propranolol between the alcohol etiology and the others.

In drug therapy, emergency of complication is an important factor in determining maintenance of medication. Avgerinos et al¹⁷ reported that complications of propranolol therapy were dizziness (9.5%), flapping tremor (4.7%), and cardiac failure (4.7%). In addition, Lay et al¹⁸ documented that 16% of patients had to withdraw from the propranolol therapy due to adverse events such as hypotension and dizziness. However, in other literatures,^{6,10} no adverse effects were observed throughout the study. In the present study, the only complication noted was dizziness: this was found in 24% of the patients treated with propranolol. However, it was not serious enough to discontinue the administration of the drug. These results suggest that propranolol could be safely used in Korea cirrhotic patients without serious adverse effect.

Recently, new therapeutic approaches are being investigated as an attempt to improve the treatment of portal hypertension.^{19,20} Over the last decades, a number of agents such as losartan, carvedilol, and nitrates have been shown to reduce the portal pressure and other agents are in the process of development or undergoing clinical trials.²¹⁻²³ Therefore, new treatments with improved survival benefit compared to propranolol should be available over time.

In conclusion, propranolol is safe and effective for the reduction of portal pressure in Korean patient with cirrhosis. To obtain an effective improvement of portal hypertension, it is necessary to increase the dose of propranolol until the target heart rate is reached when a measurement of the HVPG is not available.

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