Rifaximin and Propranolol Combination Therapy Is More Effective than Propranolol Monotherapy for the Reduction of Portal Pressure: An Open Randomized Controlled Pilot Study

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Background/Aims: Non-selective beta blockers (NSBBs) are currently the only accepted regimen for preventing portal hypertension (PHT)-related complications. However, the effect of NSBBs is insufficient in many cases. Bacterial translocation (BT) is one of the aggravating factors of PHT in cirrhosis; therefore, selective intestinal decontamination by rifaximin is a possible therapeutic option for improving PHT. We investigated whether the addition of rifaximin to propranolol therapy can improve hepatic venous pressure gradient (HVPG) response. **Methods:** Sixty-four cirrhosis patients were randomly assigned to propranolol monotherapy (n=48) versus rifaximin and propranolol combination therapy (n=16). Baseline and post-treatment HVPG values, BT-related markers (lipopolysaccharide [LPS], LPS-binding protein [LBP], interleukin-6 [IL-6], and tumor necrosis factor α [TNF-α]), serological data, and adverse event data were collected. HVPG response rate was the primary endpoint. **Results:** Combination therapy was associated with better HVPG response rates than monotherapy (56.2% vs 87.5%, p=0.034). In combination therapy, posttreatment BT-related markers were significantly decreased (LPS, p=0.005; LBP, p=0.005; IL-6, p=0.005; TNF-α, p=0.047). **Conclusions:** Rifaximin combination therapy showed an additive effect in improving PHT compared to propranolol monotherapy. These pilot data suggest that the addition of rifaximin to NSBBs could be a good therapeutic option for overcoming the limited effectiveness of NSBBs. **(Gut Liver 2017;11:702-710)**

Key Words: Bacterial translocation; Rifaximin; Hypertension, portal; Hepatic venous pressure gradient

INTRODUCTION

Various clinical manifestations, such as ascites, variceal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome develop according to the severity of portal hypertension (PHT) in advanced cirrhosis.[1,2] Among these complications, variceal bleeding is a potentially fatal complication, and even with appropriate management by endoscope and medical therapy, the mortality is about 15% to 20%.[3] Therefore, control of portal pressure and hemodynamic instability is a crucial component of cirrhosis management. Non-selective beta blockers (NSBB) are currently the only accepted regimen for reducing portal pressure,[4-6] and the goal of NSBB therapy is to reduce the hepatic venous pressure gradient (HVPG) more than 20% from the baseline value or to absolute HVPG value under 12 mm Hg.[7] However, many patients do not reach the treatment target, since only 30% to 50% of patients achieve a hemodynamic response to NSBB therapy, which is an important limitation of NSBB.[5,8,9]

Bacterial translocation (BT) is defined as the entry of viable bacteria or their products into the regional lymph nodes, the systemic circulation, and possibly extraintestinal organ.[10] BT occurs in 25% to 30% of cirrhosis patient with hepatic dysfunction,[11] and BT-related bacterial infections are closely related to PHT and hyperdynamic circulatory syndrome, therefore, control of BT is also important for cirrhosis management.

Intestinal bacterial overgrowth is a main factor promoting BT; selective intestinal decontamination by antibiotics is theoretically relevant for control of BT. Rifaximin is a gastrointestinal selective antibiotic with a broad spectrum of antimicrobial activity and it is not absorbed systemically.[12] The effectiveness of rifaximin have been proven in management of hepatic en-

cephalopathy and spontaneous bacterial peritonitis.[13-15] These results indicated that application of rifaximin was helpful for modulating BT. However, studies about the effect of rifaximin for improving PHT, which is measured by HVPG, are currently limited, even though this is one of the most reliable surrogate markers of clinical outcomes in cirrhosis patients.[16] Therefore, in the present study, we investigated additional effects of rifaximin for controlling PHT and the possible biochemical mechanism, using an open-label randomized controlled pilot study.
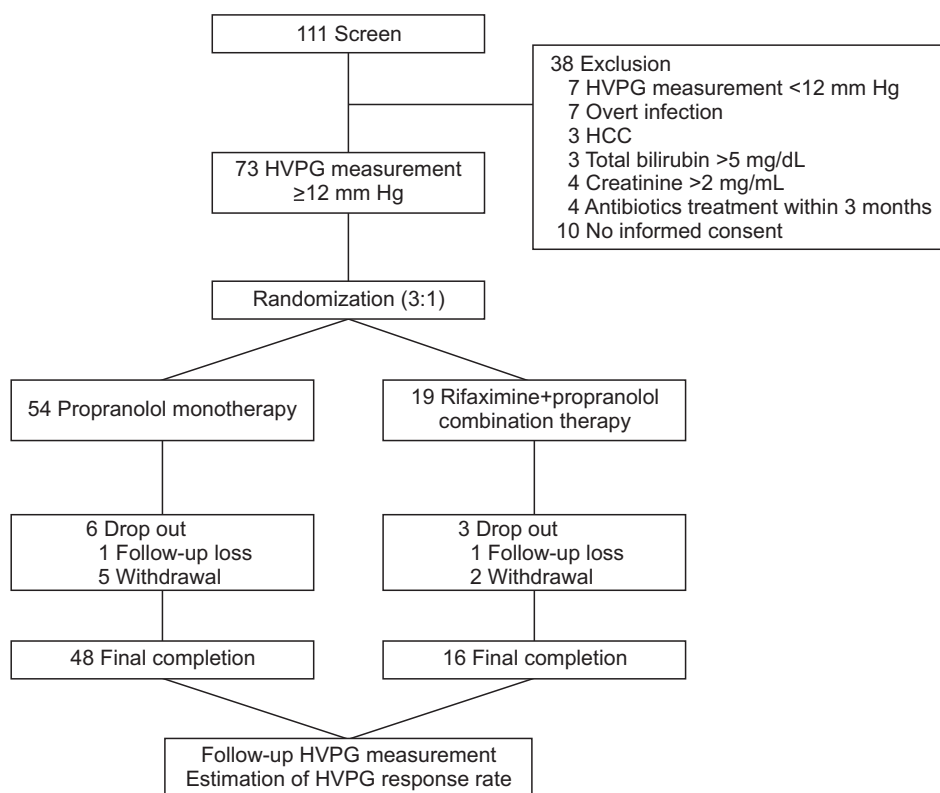
MATERIALS AND METHODS

1. Patients

Patients between 18 and 70 years of age with advanced cirrhosis who visited the Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine between January 2011 to July 2013 were considered eligible for the study. The diagnosis of cirrhosis was either liver biopsy proven or clinically suspected based on image studies that included ultrasonography and computerized tomography scans, the presence of varices in the esophagogastroduodenoscopy, and laboratory data. The enrolled patients abstained from alcohol for at least 3 months before enrollment in any cirrhosis etiology. This study included patients who showed HVPG ≥12 mm Hg among patients who required NSBB prophylaxis to prevent variceal hemorrhage, according to guidelines;[17,18] patients with small varices with Child-Pugh's class B/C or presence of red wale marks on varices, patients with medium/large varices or patients that experienced

variceal hemorrhaging. Exclusion criteria were as follows: the baseline HVPG value was less than 12 mm Hg, the presence of spontaneous bacterial peritonitis, refractory ascites, other overt clinical infections, and hepatocellular carcinoma. Patients with a baseline total bilirubin >5 mg/dL or creatinine >2 mg/mL were excluded. Patients treated with antibiotics or prebiotics during the last 3 months before enrollment in this study, and patients who refused to participate in this study were also excluded. Based on these criteria, 111 patients were considered as study candidates. Among 111 patients who were included in the original trial, 38 patients were excluded, and 73 patients were considered eligible for this study and randomly assigned to receive propranolol monotherapy (n=54) or rifaximin and propranolol combination therapy (n=19) (Fig. 1). BT related markers such as lipopolysaccharide (LPS), and LPS-binding protein (LBP), pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) were also measured at baseline in available patients.

2. Study design

This study was done prospectively as a randomized open-labeled controlled trial that was conducted at a single center in South Korea. The Institutional Review Board of the Wonju Severance Christian Hospital approved the protocol. Written informed consent to participate in the study was received from all of the participating patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Fig. 1. Flow chart of patient inclusion. HVPG, hepatic venous pressure gradient; HCC, hepatocellular carcinoma.

1) Randomization and treatment

Patients were chronologically randomized in a 3:1 fashion using a computer-generated logarithm into either the propranolol monotherapy group (54 patients) or the rifaximin and propranolol combination therapy group (19 patients). The reasons for 3:1 ratio allocation were as follows: First, rifaximin is relatively expensive and its cost was borne by patients because the long-term application of rifaximin was not supported by Korean National Health Insurance Service when this study was performed. Therefore, large population number in rifaximin group was not possible in pilot study. Second, through the previous studies, we could predict the combination group would show better outcome. Finally, previous a few studies have shown that NSBB also could be effective for reducing BT; therefore, we also needed enough numbers of propranolol alone group to confirm the relationship between BT and propranolol monotherapy. The propranolol dosage was started at 40 mg/day and titrated to a maximum of 320 mg/day with a target of 25% heart rate (HR) reduction or a HR of 55 beats per minute in both groups. In the combination therapy group, additional rifaximin dosing of 1,200 mg/day was administrated with propranolol. The duration of treatment was 3 months.

2) Primary and secondary end points

The primary end point was improvement in the HVPG response rate. The HVPG response is defined as the value of HVPG reduced more than 20% from baseline or to less than 12 mm Hg.[7] The definition of the HVPG response rate is the percent of patients who showed HVPG response in each group. The secondary end point was the change in the HVPG value, HVPG change rate, and change of BT-related markers and proinflammatory cytokines between pre- and posttreatment. Change in the HVPG value is defined as the difference between the HVPG value in pre- and posttreatment. HVPG change rate is defined as the percent of change of HVPG value of the baseline HVPG value.

3) Follow-up

Patients were followed for 3 months after randomization. During this study, patients did not receive any other medications that could influence the effect of propranolol and rifaximin. Alcohol intake was monitored every week by phone calls with patients and their family, and in their monthly visit to the hospital via liver function tests. Clinical and laboratory test follow-up, and assessment for the presence of side effects were conducted every month. In addition, during each visit, the remaining medications were also counted. During follow-up, six patients in the monotherapy group (follow-up loss, one; withdrawal, five) and three patients in combination therapy group (follow-up loss, one; withdrawal, two) dropped out of the study. After the 3 months, 48 patients in the monotherapy group and 16 patients in the combination therapy group completed treatment and entered final analysis. The HVPG, BT-related markers and proinflammatory cytokines were measured again to access the response to treatment (Fig. 1).

3. HVPG measurement

After an overnight fast, the right hepatic vein (HV) was catheterized percutaneously through the right femoral vein, and the pressure was recorded in both the free and the wedged position with a 7F balloon-tipped catheter (Arrow International, Erding, Germany). HVPG was determined by subtracting the free HV pressure from the wedged HV pressure.[19,20] All measurements were performed in at least triplicate, and permanent tracings were obtained on a multichannel recorder. An examiner (Young Joo Kim) with more than 15 years of experience in HVPG measurement performed all of the HVPG procedures and was blinded to clinical information. The coefficient of variation in HVPG measurement at our medical center was 7%. Clinically significant portal hypertension (CSPH) was defined as HVPG ≥10 mm Hg.

4. BT-related markers and proinflammatory cytokine determination

To measure BT-related markers and proinflammatory cytokines, peripheral blood samples were collected on the same date of pre- and post-treatment HVPG measurements. Blood samples were separated by centrifugation at 1,500×g for 15 minutes within 30 minutes of collection. Samples were stored at –80°C until the analysis.

To determine LPS, serum samples were diluted 1:10 with pyrogen-free water and incubated for 10 minutes at 75°C to remove serum inhibitors. The concentration of LPS in serum was analyzed using the Limulus Amebocyte Lysate (LAL) assay, a quantitative chromogenic test for detecting endotoxins (QCL-1000 LAL assay; Lonza, Walkersville, MD, USA). The lower detection limit for LPS was 0.1 EU/mL. ELISA assays were used to quantitatively measure the serum concentration of LBP (HK315; Hycult Biotech, Uden, The Netherlands), IL-6 (Human Quantikine kits; R&D Systems, Minneapolis, MN, USA), and TNF-α (Human Quantikine kits) according to the manufacturers' instructions. The absorbance at the 450-nm light wave was measured in each well with a microplate reader (BioTek ELX; BioTek, Shoreline, WA, USA). The lower limit of detection for LBP was 4.4 ng/mL, IL-6 was 0.70 pg/mL, and TNF-α was 0.5 pg/mL. All measurements were performed in duplicate and the mean value is presented.

5. Statistical analysis

Continuous variables are presented as mean±standard deviation. Categorical variables are shown as counts and proportions. Group comparisons in continuous variables were with the Independent t-test and Mann-Whitney U test, as appropriate. Categorical variables were compared with the chi-square test.

Repeated measured pre- and post-treatment values were compared with a paired t-test and Wilcoxon signed rank test, as appropriate. A p-value <0.05 was considered to be statistically significant. Statistical analysis was conducted using the IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The general characteristics are summarized in Table 1. The general clinical and biological characteristics were well-balanced between groups.

1. Rifaximin combination therapy results

The baseline HVPG value was statistically similar in both

Table 1. General Characteristics

Characteristic	Monotherapy (n=48)	Combination therapy (n=16)	p-value
Age, yr	48.79±9.66	51.19±9.58	0.393
Male sex	41 (85.4)	15 (93.8)	0.667
Etiology			0.701
Alcohol	28 (58.3)	13 (81.25)	
HBV	10 (20.8)	2 (12.5)	
Alcohol+HBV	8 (16.7)	1 (6.25)	
Alcohol+HCV	1 (2.1)	0	
Cryptogenic	1 (2.1)	0	
Child-Pugh score	7.08±1.70	6.94±2.18	0.287
MELD score	11.44±4.07	10.13±3.85	0.262
AST, U/L	65.69±35.86	70.64±43.20	0.693
ALT, U/L	39.25±59.92	30.00±21.41	0.618
Albumin, g/dL	3.00±0.35	3.01±0.43	0.671
Total bilirubin, mg/dL	2.02±1.51	3.43±7.13	0.198
Prothrombin time, INR	1.33±0.34	1.22±0.23	0.206
CRP, mg/dL	1.01±1.83	0.74±0.65	0.719
WBC, 10^9/L	5.47±2.98	5.27±1.92	0.805
PMN, 10^9/L	3.53±2.51	3.11±1.53	0.529
Platelet, 10^9/L	102.69±50.25	101.19±41.70	0.915
Hemoglobin, g/dL	10.88±2.05	11.89±1.99	0.089
Sodium, mmol/L	138.04±3.13	138.31±4.03	0.783
Creatinine, mg/dL	0.88±0.25	0.78±0.17	0.142
SBP, mm Hg	116.69±18.76	117.50±8.56	0.868
DBP, mm Hg	73.98±11.50	71.88±9.11	0.509
MBP, mm Hg	88.12±12.70	87.08±8.07	0.760
HR, beats/min	75.02±11.33	71.31±9.25	0.241
Dose of propranolol, mg/day	152±59.3	127.0±32.4	0.033

Data are presented as mean±SD or number (%).
HBV, hepatitis B virus; HCV, hepatitis C virus; MELD score, model for end-stage liver disease score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; CRP, C-reactive protein; WBC, white blood cell; PMN, polymorphonuclear leukocytes; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate.
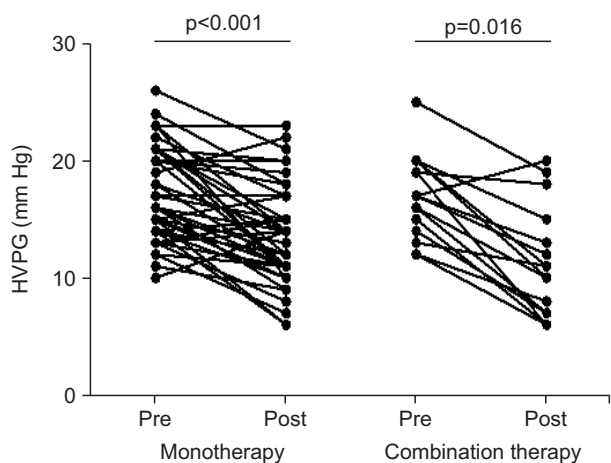
Table 2. HVPG Value and Response Rates of the Monotherapy and Combination Therapy Groups

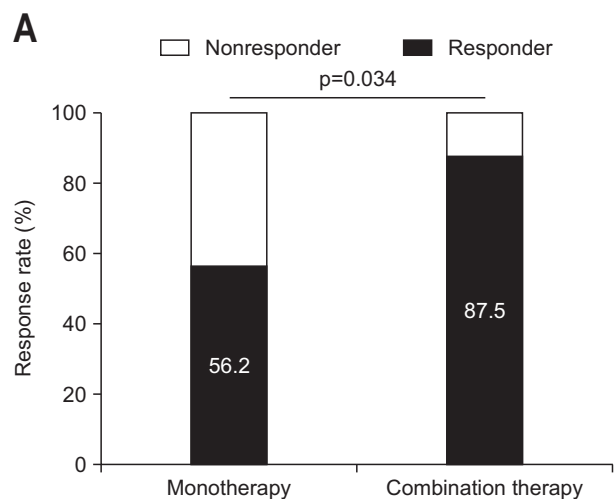|	Monotherapy (n=48)	Combination therapy (n=16)	p-value
Baseline HVPG, mm Hg	17.00±3.86	17.00±3.46	1.000
Posttreatment HVPG, mm Hg	13.52±4.06	11.19±4.71	0.060
Change in HVPG, mm Hg	3.48±3.85	5.69±4.19	0.057
HVPG change rate, %	18.93±22.90	34.75±24.21	0.022
HVPG response rate	27 (56.2)	14 (87.5)	0.034

Data are presented as mean±SD or number (%).
HVPG, hepatic venous pressure gradient.

groups (p=1.000) (Table 2). After treatment, portal pressure declined significantly in both groups (monotherapy, 17.00±3.86 to 13.52±4.06 mm Hg, p<0.001; combination therapy, 17.00±3.46 to 11.19±4.71 mm Hg; p=0.016) (Fig. 2). After the treatment, the HVPG response rate was significantly greater in the combination therapy group than in the monotherapy group (27/48 patients [56.2%] vs 14/16 patients [87.5%], p=0.034) (Table 2, Fig. 3A). The change in the HVPG value decreased in the combination therapy group compared with the monotherapy group (3.48±3.85 mm Hg vs 5.69±4.19 mm Hg, p=0.057). The HVPG change rate was also significantly greater in the combination therapy group than in the monotherapy group (18.93%±22.90% vs 34.75%±24.21%, p=0.022) (Fig. 3B).

Fig. 2. Pretreatment and posttreatment hepatic venous pressure gradient (HVPG) value comparisons between the propranolol monotherapy group and the combination therapy group (monotherapy group, 17.00±3.86 to 13.52±4.06 mm Hg, p<0.001; combination therapy group, 17.00±3.46 to 11.19±4.71 mm Hg, p=0.016).
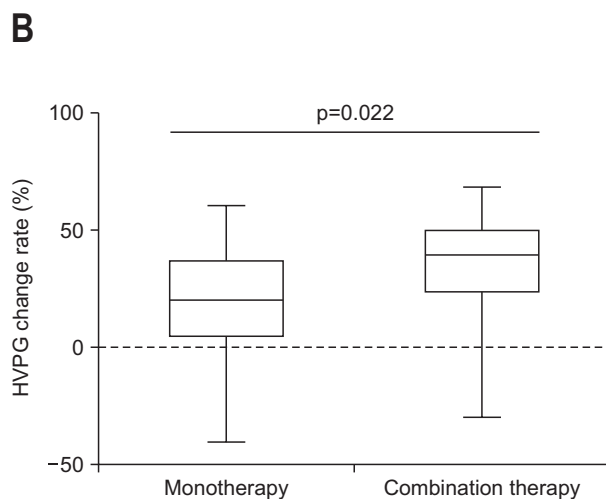Pre, pretreatment; Post, posttreatment.

2. Rifaximin combination therapy for BT-related markers and proinflammatory cytokines

The BT-related markers and proinflammatory cytokines were measured for 13 patients in the monotherapy group and 10 patients in the combination therapy group. The baseline LPS, LBP, IL-6, and TNF-α were not significantly different between the groups. All BT-related markers and proinflammatory cytokines decreased after treatment regardless of therapy. In the combination therapy group, all BT-related markers and proinflammatory cytokines showed statistically significant decreases after treatment (LPS, p=0.005; LBP, p=0.005; IL-6, p=0.005; TNF-α, p=0.047) (Table 3). In the monotherapy group, all BT-related markers and proinflammatory cytokines also decreased after treatment (LPS, p=0.064; LBP, p=0.055; IL-6, p=0.007; TNF-α, p=0.064) (Table 3). The change rates of LPS and LBP between the pre- and post-treatment were significantly higher in the combination therapy group than in the monotherapy group (LPS, p=0.009; LBP, p=0.002); however, IL-6 and TNF-α results were not statistically significant (Table 3).

In subgroup analysis for NSBB responders, LPS, LBP, and IL-6 significantly decreased (LPS, p=0.008; LBP, p=0.008; IL-6, p=0.008), and TNF-α also showed a decreasing trend after treatment (p=0.051) in the combination therapy group (Table 4). In the monotherapy group, LPS and IL-6 significantly decreased after treatment (LPS, p=0.028; IL-6, p=0.005), and LBP also had a decreasing trend after treatment (p=0.059) (Table 4).

3. Safety

No significant difference in baseline systolic blood pressure, diastolic blood pressure, and mean blood pressure (MBP) between the monotherapy group and the combination therapy group were observed (Table 1). The reduction in MBP after

Fig. 3. (A) Comparison of the hepatic venous pressure gradient (HVPG) response rate between the monotherapy and combination therapy groups (56.2% vs 87.5%, p=0.034). (B) HVPG change rate between the monotherapy and combination therapy groups (18.93%±22.90% vs 34.75%±24.21%, p=0.022).

Table 3. BT-Related Markers and Proinflammatory Cytokine Comparison between the Monotherapy and Combination Therapy Groups

	Monotherapy (n=13)				Combination therapy (n=10)				p-value[‡]
	Pretreatment	Posttreatment	Change rate, %*	p-value[†]	Pretreatment	Posttreatment	Change rate, %*	p-value[†]	
LPS, EU/mL	1.37±0.38	1.29±0.48	5.99±25.21	0.064	1.48±0.77	0.86±0.29	34.37±20.83	0.005	0.009
LBP, ng/mL	20.84±2.77	19.08±3.93	8.58±14.25	0.055	21.04±2.36	15.51±3.05	26.62±8.56	0.005	0.002
IL-6, pg/mL	9.65±3.33	5.52±4.03	42.85±27.82	0.007	10.31±4.53	4.78±2.86	52.76±22.05	0.005	0.366
TNF-α, pg/mL	4.35±1.03	3.85±0.88	9.14±20.12	0.064	4.52±0.54	3.83±0.87	14.63±19.49	0.047	0.518

Data are presented as mean±SD.
BT, bacterial translocation; LPS, lipopolysaccharide; LBP, LPS-binding protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor α.
*The rate of change is defined as the percent difference between the pre- and posttreatment values of BT-related markers and proinflammatory cytokines; [†]p-values for the differences between pre- and posttreatment BT-related markers and proinflammatory cytokines; [‡]p-value of the differences in the rate of change of BT-related markers and proinflammatory cytokines between the monotherapy and combination therapy groups.

Table 4. BT-Related Markers and Proinflammatory Cytokine Comparisons of Hemodynamic Responders in the Monotherapy and Combination Therapy Groups

	Monotherapy (n=10)			Combination therapy (n=8)		
	Pretreatment	Posttreatment	p-value	Pretreatment	Posttreatment	p-value
LPS, EU/mL	1.26±0.28	1.09±0.21	0.028	1.45±0.81	0.78±0.15	0.008
LBP, ng/mL	19.96±2.08	17.82±3.44	0.059	20.52±1.80	14.94±2.62	0.008
IL-6, pg/mL	9.34±3.44	4.22±1.55	0.005	9.89±4.58	4.58±2.95	0.008
TNF-α, pg/mL	4.36±1.12	3.80±0.93	0.139	4.51±0.58	3.73±0.87	0.051

Data are presented as mean±SD.
BT, bacterial translocation; LPS, lipopolysaccharide; LBP, LPS-binding protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor α.

treatment did not vary between the two groups (4.43±12.31 mm Hg vs 2.23±11.52 mm Hg, p=0.532). The baseline HR was similar in both groups (75.02±11.33 beats/min vs 71.31±9.25 beats/min, p=0.241) (Table 1), and the HR reduction rate was not significantly different in the two groups (16.19±11.21 beats/min vs 15.13±10.70 beats/min, p=0.634). Dizziness and other NSBB related orthostatic hypotension symptoms were observed in eight patients in the monotherapy group and two patients in the combination therapy group. Rifaximin-related severe adverse events were not observed.

DISCUSSION

In this study, we analyzed the effectiveness of rifaximin and propranolol combination therapy compared with the standard propranolol monotherapy and the impact of this treatment based on hemodynamic (HVPG value) and nonhemodynamic effects (BT-related markers and proinflammatory cytokines).

NSBB is the only generally recommended medication for primary and secondary prevention of variceal bleeding.[21] Although recently some arguments have been published on the application of NSBB in the advanced cirrhosis, there is still evidence that indicates that NSBB can help prevent other PHT-related complications such as ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.[5,16,22] However, these positive data were almost all derived from NSBB

responders who were identified by estimating hemodynamic response by the HVPG measurement, and the NSBB response rate was only one-third to one-half in these specific cases.[5,23] Although there have been many trials to improve the low efficacy of NSBB and to identify another more effective agent, no other alternative treatment has been generally accepted, until now.

BT is a critical factor that triggers host immune response and increases serum levels of endotoxin and proinflammatory cytokines that promote hepatic fibrosis and PHT.[11,24-26] In comparison, PHT promotes BT and endotoxemia due to impaired host immune response, increased bacterial overgrowth and intestinal permeability.[25] Therefore, PHT and BT have reciprocal interactions and controlling BT has been a focus for controlling PHT. Intestinal decontamination using norfloxacin has shown promising results;[27] however, the development of quinolone resistant bacteria and extended-spectrum ß-lactamase-producing bacteria prevents safe long-term use of norfloxacin.[28,29]

Rifaximin is an antibiotic with broad antimicrobial, high fecal concentration, and low systemic absorption.[12,30] In cirrhotic patients, the effectiveness of rifaximin has been investigated in many clinical trials that have addressed hepatic encephalopathy remission and prevention.[15,31] In a previous study, Vlachogiannakos et al.[32] identified the possibility of rifaximin as a new candidate for controlling PHT based on the results of a single arm study that used rifaximin and HVPG measurement. However, recently, Kimer et al.[33] reported opposite results with

similar design through the randomized controlled trial. They showed that rifaximin therapy is not effective to control hemodynamics in the advanced cirrhosis. This is also opposite finding with our present study results. The reasons that rifaximin effect was different can be found in several different points between Vlachogiannakos' or Kimer's study and our present study. In contrast to rifaximin monotherapy in previous studies, we basically applied propranolol to both group and added rifaximin only to combination group in the present study. It is very important point. Even though rifaximin is expected to control BT, we think that rifaximin alone is not enough to reduce HVPG because PHT and sequential hemodynamic changes are not just results of BT but many other more important factors also affect it. Therefore, in this study, we focused on the additional effect of rifaximin in the propranolol-based anti-PHT treatment. In the context, the target population is also different. The present study basically targeted the control of variceal hemorrhage risk based on HVPG values and therefore, this study includes relatively small numbers of ascites patients (11 patients, seven in monotherapy and four in combination group).

In the present study, the rifaximin and propranolol combined therapy led to a significantly higher hemodynamic response rate compared to the propranolol monotherapy group (HVPG response rate, 87.5% vs 56.2%, p=0.034). Even though the propranolol monotherapy response rate in our institution was not bad compared to generally reported data, the difference in treatment groups was apparent. In addition, the change rate of HVPG after treatment between the two groups was also significantly different (p=0.022). These findings suggest that suppression of BT using rifaximin actually resulted in an improved HVPG response rate. The results also indicated that control of BT and the nonhemodynamic effect could be another important target for controlling PHT, and that BT can be controlled which can induce additional effects for controlling PHT in clinical practice.

Improvement in the hemodynamic response using rifaximin was also confirmed by BT-related biomarkers and proinflammatory cytokines (LPS, LBP, IL-6, and TNF-α). These results were significant even though the analyzed serum samples were relatively small, because this study was pilot design (combination therapy group, n=10; monotherapy group, n=13). We directly analyzed the relationship between hemodynamic responsiveness and BT-related biomarkers and proinflammatory cytokines changes. All of the BT-related markers and proinflammatory cytokines showed statistically significant decreases after rifaximin treatment (Table 3). In the hemodynamic responders in the combined group, LPS, LBP, and IL-6 showed significant decreases after treatment (Table 4); however, in the non-responders there was no significant change. These findings were similar in the propranolol monotherapy group, and the hemodynamic responders also showed significant decreases in the LPS, IL-6 and trends in LBP. These results suggest that the control of BT

and the changes of BT-related biomarkers and proinflammatory cytokines can be a critical factor for determining hemodynamic responsiveness, irrespective of treatment group. This also provides a basis for understanding the prognosis and clinical implications of hemodynamic nonresponders and correlations with the BT response. In a previous review, approximately 40% of hemodynamic nonresponders do not show rebreeding and the BT prevention effect of NSBB has been suspected to be the main factor for this finding and which is going to be important issue for future clinical research to address.[34]

Recently, some investigators showed that NSBB alone can be helpful for preventing BT and BT-related infection, ACLF by improved sympathetic tone, intestinal motility and decreased intestinal permeability.[8,35] In this study, the propranolol monotherapy group was also associated with a preventive effect of BT and a decrease in BT-related biomarkers and proinflammatory cytokines (Table 3). Although this effect was relatively small compared with the correlations in rifaximin combination therapy, it also showed the possibility that NSBB alone can impact on BT. With the present data, we cannot estimate the proportion of BT and its contribution to PHT, particularly for validating and clarifying the recent "Window Theory of NSBB" that has been identified.[16] Therefore, additional studies are needed to determine the longitudinal effect of NSBB-induced BT responsiveness.

MBP was mildly reduced after treatment, in both groups, and some patients had orthostatic hypotension symptoms, although no serious adverse events were identified. In previous studies, the adverse events related to receiving rifaximin included nausea, diarrhea, abdominal discomfort, fatigue, and these results were not clinically significant.[36,37] In our study, serious adverse events related to receiving rifaximin was not identified during the follow-up period.

There are several limitations to this study even though this was performed as a pilot study. First, the allocation of monotherapy and combination therapy group was three to one, so combination group includes relatively small numbers of patients. Second, the small sample size and numbers of serum analysis is also limitation. However, this was a well-designed randomized controlled trial and it can be used as a basis data for a large-scale, double-blind RCT (NCT01897051). Finally, the mean dose of propranolol in monotherapy and combination group were 152±59.3 mg and 127.0±32.4 mg (p=0.033), respectively. The reason why there is statistical difference is not clear and we could not explain logically through this study. This finding is not enough to support that rifaximin also has propranolol dose reduction effect. Some changes of bacterial colonization and composition can be related with the change of pharmacokinetics and effect of propranolol; however, more accurate pharmacological investigation and validation should be preceded.

In conclusion, we analyzed the effectiveness of rifaximin

and propranolol combination therapy compared to standard propranolol monotherapy on the point of hemodynamic effect (HVPG value) and nonhemodynamic effect (BT-related markers and proinflammatory cytokines). The addition of rifaximin showed an additive effect for reducing HVPG through stronger prevention of BT than standard propranolol monotherapy. Therefore, administration of rifaximin with propranolol in CSPH patients to reduce HVPG can be applied as a therapeutic option for management of portal hypertensive complications and to overcome the limitations of NSBB.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

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