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Propranolol plus endoscopic ligation for variceal bleeding in patients with significant ascites

Propensity score matching analysis

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Abstract

The use of beta-blockers in decompensated cirrhosis accompanying ascites is still under debate. The aim of this study was to compare overall survival (OS) and incidence of cirrhotic complications between endoscopic variceal ligation (EVL) only and EVL + non-selective beta-blocker (NSBB) combination therapy in cirrhotic patients with significant ascites (≥grade 2).

This retrospective study included 271 consecutive cirrhotic patients with ascites who were treated with EVL only or EVL + NSBB combination therapy as a primary prophylaxis of esophageal varices. The primary outcome was all-cause mortality. Propensity score matching was performed between the 2 groups to minimize baseline difference.

Median observation period was 42.1 months (interquartile range, 18.4–75.1 months). All patients had deteriorated liver function: 81.1% Child-Pugh class B and 18.9% Child-Pugh class C. All-cause mortality was significantly higher in the EVL + NSBB group than in the EVL only group not only in non-matched cohort, but also in matched cohort (48.9% vs 31.2%; $P = .039$). More people died from hepatic failure in the EVL + NSBB group than that in the EVL only group (40.5% vs 20.0%; $P = .020$). However, the incidence of variceal bleeding, hepatorenal syndrome (HRS), or spontaneous bacterial peritonitis (SBP) was not significantly different between the 2 groups.

The use of NSBB might worsen the prognosis of cirrhotic patients with significant ascites. These results suggest that EVL alone is a more appropriate treatment option for prophylaxis of esophageal varices than propranolol combination therapy when patients have significant ascites.

Abbreviations: EVL = endoscopic variceal ligation, HRS = hepatorenal syndrome, NSBB = non-selective beta-blocker, OS = overall survival, PSM = propensity score matching, SBP = spontaneous bacterial peritonitis.

Keywords: ascites, beta blocker, endoscopic variceal ligation

1. Introduction

In patients with cirrhosis and esophageal varices, the incidence of variceal bleeding is about 12% to 15% per year.[1] Mortality rate due to bleeding is still high up to 20%.[2,3] Mortality of variceal bleeding is usually determined by size of varices or basal liver function.[4] According to the Baveno VI guideline, there are 2 major axes of primary prophylaxis for varices: non-selective beta-blockers (NSBB) and endoscopic band ligation (EVL).[5] EVL is a physical method that rarely causes hemodynamic changes. On the contrary, NSBB can cause hemodynamic changes by reducing cardiac output and vasodilation.[6] In this context, it is unclear so far whether the use of NSBB is beneficial for end-stage liver disease.[5,7] Serste et al[6] have announced the risk of NSBB and introduced the window hypothesis which addresses the optimal period of NSBB use during natural course of liver cirrhosis.[4] They have suggested that NSBB should be used with caution in decompensated cirrhosis. However, this is still an unresolved argument as many reports have suggested that NSBB may be helpful, even in decompensated state or refractory ascites. For example, it has been shown that NSBB is helpful in the prognosis of spontaneous bacterial peritonitis (SBP) by reducing inflammation and that it can improve prognosis of patients awaiting liver transplantation.[8] However, most papers that report the advantage of NSBB used short-term observation period within 6 months on average.[9,10] Considering that the mean survival of patients with varices is approximately 2 years, it is difficult to apply such positive result of short-term studies directly to clinical practice.

Ascites is one of the most common complications of cirrhotic patients. We frequently encounter patients with both ascites and varices in clinical practice. It is currently unknown whether NSBB

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is useful or harmful for patients with ascites and varices. The current guidelines did not clarify what treatment should be done with primary prophylaxis for varices either. Therefore, the objective of this study was to analyze long-term outcome of EVL only and EVL + NSBB combination therapy as primary prevention of varices in patients with significant ascites using real practice clinical data.

2. Materials and methods

2.1. Patients and study protocol

Between January 2005 and December 2016, we collected consecutive data of Child B or C patients with cirrhosis and ascites during routine clinical care in a tertiary hospital (SoonChunHyang University Bucheon Hospital; Bucheon, Korea). Among them, patients who fulfilled the following inclusion criteria were eligible for this study: those who received EVL or propranolol treatment for primary prevention of esophageal varices, the presence of grade II or III ascites at the time of initial treatment for esophageal varices. Patients were excluded if they met the following exclusion criteria: history of variceal bleeding prior to treatment, liver cancer or other malignancy possible to cause ascites, patients having ascites not caused by liver disease, use of other NSBBs (e.g., carvedilol) or period of NSBB use <4 weeks, and those who underwent liver transplantation. Finally, we divided patients into EVL + propranolol group or EVL alone group to see if clinical outcome would be different according to their treatment modality.

Clinical and laboratory records of all patients were retrospectively reviewed. The diagnosis of cirrhosis was established on the basis of clinical, biochemical, radiologic, or histologic evidence. The diagnosis of hepatorenal syndrome (HRS) was performed retrospectively by reviewing all patients ICD (international classification of disease) code, and also checking the history of terlipressin use. In Korea, terlipressin is prescribed very strictly only for HRS patients and reimbursed by the national health insurance system. The diagnostic criteria of HRS reimbursed by the national health insurance system is similar as those for 2015 International Club of Ascites guideline.[11] When patients were stable, blood tests were performed at 3 months interval and ultrasound was performed at 6 months interval at the outpatient clinic. The study protocol was approved by the Institutional Review Board of Soon Chun Hyang University Bucheon Hospital (IRB No. 2019–03–011). The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki.

2.2. Treatment modality

Propranolol was administered to all patients if they did not have contraindications or side effects for beta-blocker such as hypotension (initial systolic blood pressure <100 mmHg) (n = 16), bronchial asthma or chronic obstructive pulmonary disease (n = 14), uncontrolled diabetes (n = 12), bradycardia (initial basal heart rate < 55 beats/min) (n = 9), cardiac conduction abnormalities (n = 4), major depression (n = 3), Raynaud phenomenon (n = 3), hypoglycemia (n = 2), heart failure (n = 2), thyrotoxicosis (n = 1), or refusal to use the drug due to easy fatigability or severe orthostatic hypotension (n = 29). Propranolol was started at a dose of 20 mg twice a day. Its dose was increased until therapeutic goal (resting heart rate of 55–60 beats per minute and systolic blood pressure not decreased to be <90 mmHg) was reached. EVL was performed every 2 to 8 weeks until the eradication of varices was achieved. Follow-up esophagogastroscopy was performed at 1-year interval.

2.3. Statistical analysis

All-cause mortality was the primary endpoint. Secondary outcomes included variceal bleeding and the development of HRS or SBP. Frequencies and percentages were used for descriptive statistics. Statistical differences between groups were investigated using the chi-squared test or Fisher exact test for categorical variables and Student *t* test or Mann–Whitney *U* test for continuous variables. Kaplan–Meier survival analysis was used to calculate the cumulative incidence of primary outcome. Propensity score matching (PSM) analysis was done to minimize the probability of selection bias by pairing EVL + propranolol group and EVL only group based on propensity score. Propensity score represents a subject's probability of being assigned to a particular treatment, conditional on observed baseline covariates. It is a recognized method of controlling for selection bias.[12,13] PSM for EVL + propranolol versus EVL only was generated by multiple logistic regression analysis. This model included all variables with clinical relevance to mortality (age, sex, etiology, grade of esophageal varices, grade of ascites, Child-Pugh class, serum creatinine). We used the nearest available matching (1:1) method on the estimated PSM. Balance was achieved after matching between EVL + propranolol group and EVL only group (Supplement Figure 1, http://links.lww.com/MD/D681). All statistical analyses were performed using R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < .05$.

3. Results

3.1. Baseline characteristics

Baseline demographic and clinical characteristics of patients are summarized in Table 1. A total of 271 patients who received primary prophylaxis for esophageal varices were analyzed. Median observation period was 42.1 months [interquartile range, (IQR) 18.4–75.1 months]. There were 197 (72.7%) men and 74 (27.3%) women. The mean age of patients was 53.8 ± 9.9 years. Non-viral etiology of liver cirrhosis was predominant. Esophageal varices grade 2 or 3 accounted for about 89%. All patients presented with significant ascites, with grade 3 ascites accounting for 18.8%. All the patients showed deteriorated liver function: 81.3% as Child-Pugh class B and 18.7% as Child-Pugh class C.

Of the 271 patients, 264 (97.4%) took diuretics. Seven patients did not take diuretics because of elevated serum creatinine levels. Respectively, 98.0%, 96.6% of the patients in the EVL group and in the combined group have used diuretics, and there was no significant difference between the 2 groups ($P = .864$). Of the 271 patients, 44 patients (16.2%) underwent intermittent paracentesis with diuretics-refractory ascites. There was no significant difference between the 2 groups; EVL group 14.7% (14 of 95) versus combination group 17.0% (30 of 176) ($P = .243$).

According to treatment method, esophageal varices grade 2 or 3 was higher in the EVL only group than that in the combination treatment group. In addition, baseline serum sodium, serum albumin, and prothrombin time international normalised ratio values were significant different between the 2 groups. To compensate for these baseline differences, we performed PS

Table 1

Baseline characteristics of patients in unmatched and matched cohort.

	Unmatched				Matched			
Variable	Total (N=271)	EVL (N=95)	EVL+BB (N=176)	*P*-value	Total (N=252)	EVL (N=80)	EVL+BB (N=172)	*P*-value
Age, y	53.8±9.9	54.4±8.5	53.6±10.6	.284	53.9±9.8	54.1±7.9	53.8±10.6	.548
Male	197 (72.7%)	66 (69.5%)	131 (74.4%)	.465	184 (73.0%)	57 (71.2%)	127 (73.8%)	.781
Etiology				.324				
Viral	116 (42.8%)	45 (47.4%)	71 (40.3%)		106 (42.1%)	36 (45.0%)	70 (40.7%)	.612
Non-viral	115 (57.2%)	50 (52.6%)	105 (59.7%)					
Esophageal varices grade				.023				.107
Grade 1	31 (11.4%)	4 (4.2%)	27 (15.3%)		28 (11.1%)	4 (5.0%)	24 (14.0%)	
Grade 2	124 (45.8%)	47 (49.5%)	77 (43.8%)		114 (45.2%)	38 (47.5%)	76 (44.2%)	
Grade 3	116 (42.8%)	44 (46.3%)	72 (40.9%)		110 (43.7%)	38 (47.5%)	72 (41.9%)	
Hemoglobin	10.6±2.3	10.9±2.5	10.4±2.1	.110	10.5±2.2	10.6±2.4	10.4±2.1	.686
Platelet	84.5±46.3	85.9±54.4	83.8±41.5	.724	84.9±46.7	86.3±56.2	84.3±41.7	.695
AST	82.9±125.2	66.2±58.6	91.8±148.6	.060	86.0±129.2	72.0±61.8	92.6±150.3	.487
ALT	43.0±73.3	37.7±41.0	45.8±85.9	.604	44.4±75.8	40.0±44.0	46.4±86.8	.412
Creatinine	1.0±0.8	1.0±1.0	1.0±0.6	.35	1.0±0.6	0.9±0.5	1.0±0.6	.19
Na	137.5±4.2	138.3±3.9	137.0±4.4	.005	137.4±4.2	138.0±4.1	137.2±4.3	.073
Albumin	3.1±0.5	3.2±0.5	3.0±0.5	<.001	3.0±0.5	3.0±0.4	3.0±0.5	.466
Total bilirubin	2.9±4.2	2.6±4.0	3.0±4.2	.263	2.9±4.2	2.9±4.3	3.0±4.2	.915
PT INR	1.4±0.3	1.3±0.2	1.4±0.3	.014	1.4±0.3	1.4±0.2	1.4±0.3	.439
Ascites				.999				
Grade 2	220 (81.2%)	77 (81.1%)	143 (81.2%)					
Grade 3	51 (18.8%)	18 (18.9%)	33 (18.8%)		48 (19.0%)	17 (21.2%)	31 (18.0%)	.664
Child-Pugh class				.269				.168
Class B	220 (81.1%)	75 (79.0%)	145 (82.4%)		205 (81.3%)	61 (76.3%)	144 (82.7%)	
Class C	51 (18.9%)	20 (21.1%)	31 (17.6%)		47 (18.7%)	19 (23.8%)	28 (16.3%)	

Data are reported as mean±standard deviation for continuous variables and n (%) for categorical variables.

ALT=alanine aminotransferase; AST=asparate aminotransferase; BB=beta-blocker; EVL=esophageal band ligation; INR=international normalised ratio; PT=prothrombin time.

P-values were calculated by Student *t* test or Mann–Whitney *U* test for continuous variables and chi-square test or Fisher exact test for categorical variables.

matching as described in the method section (Table 1). After PS matching, baseline differences between the 2 groups were diminished. Median observation period of the matched cohort was 39.6 months (IQR, 17.0–67.5 months). Other characters such as age and sex were similar to those of unmatched cohort.

3.2. Comparison of mortality according to treatment modality

First, we examined whether survival rates differed according to treatment method (Table 2). During the observational period, a total of 108 (39.9%) patients died. All-cause mortality was higher in the EVL + propranolol group than that in the EVL only group, even after PS matching (45.9% vs 31.2%, $P=.039$). Such higher mortality in the EVL + propranolol group sustained throughout the observation period (Fig. 1A, all $P<.001$). The same result was obtained after PS matching (Fig. 1B, $P=.008$).

3.3. Incidence of post EVL ulcer bleeding and cirrhotic complications after procedure

Two post EVL ulcer bleeding occurred in the combination group, and none in the EVL only group ($P=.378$). All the patients improved after conservative treatment and were successfully discharged. Conservative therapy was consisted of 2-days fasting, intravascular fluid therapy, and proton pump inhibitor. Next, we compared the incidence of cirrhotic complications, for example, variceal bleeding, HRS, and SBP, to see if these complications would happen in relation to each treatment modality (Table 2). The secondary outcome, variceal bleeding, occurred in 19.9% of patients, without showing difference between EVL only group and EVL + propranolol combination group. Frequencies of HRS and SBP known to be associated with the use of propranolol were also investigated. However, they showed no significant difference between the 2 groups. These parameters were analyzed in the PS matching group. Results revealed that variceal bleeding, HRS, and SBP showed no significant difference between the 2 groups.

Table 2

Comparison of clinical outcomes and mortality in unmatched and matched cohort.

	Unmatched cohort				Matched cohort			
Variable	Total (N=271)	EVL (N=95)	EVL+BB (N=176)	*P*-value	Total (N=252)	EVL (N=80)	EVL+BB (N=172)	*P*-value
Variceal bleeding	54 (19.9%)	17 (17.9%)	37 (21.0%)	.649	54 (21.4%)	17 (21.2%)	37 (21.5%)	.999
Hepatorenal syndrome	23 (8.5%)	7 (7.4%)	16 (9.1%)	.797	21 (8.3%)	6 (7.5%)	15 (8.7%)	.935
Spontaneous bacterial peritonitis	6 (2.2%)	2 (2.1%)	4 (2.3%)	.999	5 (2.0%)	2 (2.5%)	3 (1.7%)	.999
All-cause mortality	108 (39.9%)	25 (26.3%)	83 (47.2%)	.001	104 (41.3%)	25 (31.2%)	79 (45.9%)	.039

BB=beta-blocker, EVL=esophageal band ligation.

Data are reported as n (%) for categorical variables. *P*-values were calculated by Fisher exact test for categorical variable.

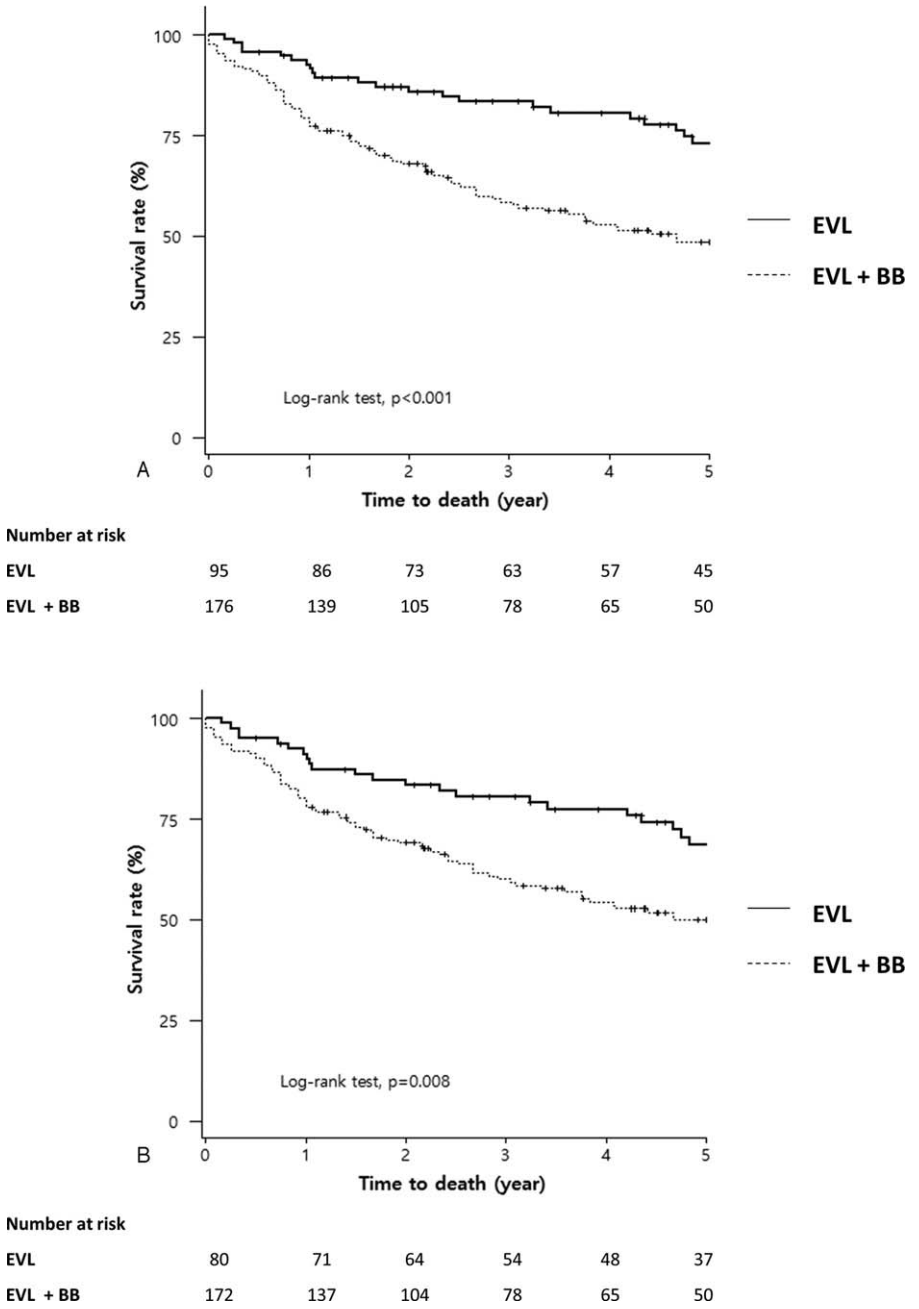

Figure 1. Kaplan–Meier curves for the survival of patients with cirrhosis and significant ascites in EVL only and EVL + BB combination groups. Use of beta-blocker in addition of EVL was associated with higher mortality both in (A) non-matched cohort and (B) matched cohort. *P*-values <.05 were considered significant. BB = beta-blocker, EVL = endoscopic variceal ligation.

3.4. Comparison of the cause of death

The cause of death was investigated to see why the difference in survival rate between the 2 groups occurred (Table 3). The proportion of death due to variceal bleeding was slightly higher in the EVL only group than that in the EVL + propranolol combination group. The difference between the two was not statistically insignificant. However, the proportion of deaths due to liver failure was significantly higher in the EVL + propranolol combination group both in the non-matched cohort and the matched cohort. Otherwise, there was no significant difference in mortality due to infection, hepatocellular carcinoma, or others between the 2 groups

Finally, we investigated the difference in mortality rate according to the dose of propranolol in the combination group (Fig. 2). There was no significant difference in mortality between the 2 groups when patients were divided into 2 groups: those who took propranolol at >80 mg and those who did not ($P = .919$). Results were similar when propranolol at dose of 160 mg was analyzed.

4. Discussion

Results of this study revealed that EVL alone as a primary prophylaxis of varix had efficacy comparable to adding propranolol to EVL in cirrhotic patients with significant ascites. However, it was safer than the combination therapy. We had 2

Table 3

Cause of death in unmatched and matched cohort.

	Unmatched cohort				Matched cohort			
Cause of death	Total (N = 108)	EVL (N = 25)	EVL+BB (N = 83)	*P*-value	Total (N = 104)	EVL (N = 25)	EVL+BB (N = 79)	*P*-value
Gastrointestinal bleeding	13 (12.0%)	4 (16.0%)	9 (10.8%)	.487	12 (11.5%)	4 (16.0%)	8 (10.1%)	.423
Hepatic failure	38 (35.2%)	5 (20.0%)	33 (39.8%)	.049	38 (36.5%)	5 (20.0%)	32 (40.5%)	.020
Cardiovascular disease	2 (1.9%)	1 (4.0%)	1 (1.2%)	.079	2 (1.9%)	1 (4.0%)	1 (1.3%)	.120
Sepsis	9 (8.3%)	2 (8.0%)	7 (8.4%)	.945	9 (8.7%)	2 (8.0%)	7 (8.9%)	.893
Hepatocellular carcinoma	7 (6.5%)	1 (4.0%)	6 (7.2%)	.565	6 (5.8%)	1 (4.0%)	5 (6.3%)	.663
Non-liver-related cause	10 (9.3%)	3 (12.0%)	7 (8.4%)	.589	10 (9.6%)	3 (12.0%)	7 (8.9%)	.642
Unknown	29 (26.8%)	9 (36.0%)	20 (24.2%)	.154	27 (26.0%)	9 (36.0%)	19 (24.0%)	.437

BB = beta-blocker, EVL = esophageal band ligation.

Data are reported as n (%) for categorical variables. *P*-values were calculated by Fisher exact test for categorical variables.

important clinical findings through this study. First, in terms of survival, we found that EVL + propranolol combination was associated with an increased risk of morality than EVL alone. Second, in terms of bleeding, the incidence of variceal bleeding was similar between the 2 groups. Mortality related to bleeding was a little lower in the EVL + propranolol combination group, although the difference between the 2 was not statistically significant. Unlike previous reports that NSBB can be used safely in patients with ascites, our study reported a better prognosis of endoscopic treatment. This study may provide additional information in the area of prophylactic treatment of esophageal varices for cirrhotic patients with significant ascites, which is not yet well established.

According to Baveno guideline VI, combined treatment is recommended for secondary prophylaxis. On the other hand, either NSBB or EVL is recommended in primary prophylaxis. However, the choice of treatment is based on expert opinion, and the evidence level is very low. Furthermore, the number of studies comparing EVL only and EVL + propranolol combination as primary prophylaxis of esophageal varix is far fewer than that of secondary prevention studies, especially in patients with significant ascites. Particularly, few research studies have been conducted on cirrhotic patients with significant ascites. According to a meta-study published by Njei et al,[14] 10 studies on the prophylaxis of esophageal varices in patients with ascites have been published so far. All of these studies have <200 cirrhotic patients having ascites, which is fewer than our study. A previous study by Sarin et al[15] conducted on primary prophylaxis concluded that adding propranolol to an EVL did not lower bleeding (7% vs 11%) or death (8% vs 15%). However, patients with ascites comprised only about half of these subjects. In addition, their observation period was shorter than our study.[15]

NSBB has both hemodynamic and non-hemodynamic effects.[3] It hemodynamically reduces the portal inflow. It also directly decreases the variceal flow, thus reducing variceal growth and blocking the occurrence of collateral circulation.[16–18] In non-hemodynamic aspects, NSBB could play a positive role by reducing bacterial translocation and inflammation, thus reducing SBP, hepatic encephalopathy, and overall survival.[8,19]

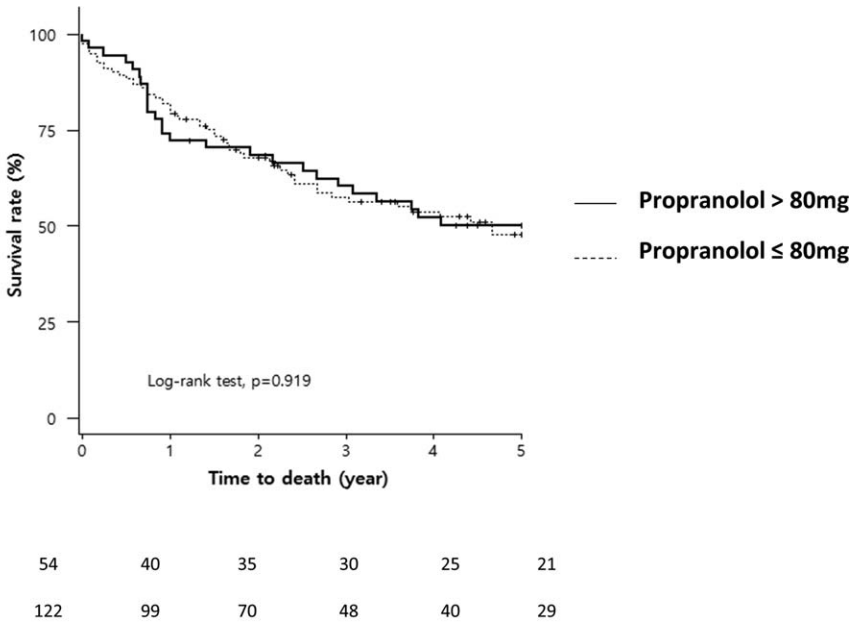

Figure 2. Kaplan–Meier curves of propranolol dose. Patients who used propranolol at dose below 80 mg/d had similar mortality risk compared with those who used propranolol at dose above 80 mg/d.

However, there is a continuing conflicting report as to whether NSBB is safe in far advanced cirrhosis. This discrepancy may be due to different observation periods and uncontrolled biases in each study. From the standpoint of advocating the use of NSBB, the use of NSBB has been associated with decreased liver transplantation and increased survival in patients with advanced liver cirrhosis.[20] Recently, a meta-analysis consisting of 9 studies on patients with any grade of ascites reported that the use of NSBB did not increase mortality.[14] There are 2 studies involving >100 patients. They published positive effects of NSBB. However, their observation period was very short, with a median of 1 to 2.4 months.[9,10] On the other hand, carvedilol did not increase mortality in long-term use (median 2.3 years) in patients with moderate or severe ascites. It even decreased mortality in mild ascites.[21]

Those who oppose the use of NSBB in decompensation believe that NSBB may theoretically further worsen the hemodynamic state by suppressing the compensatory mechanism of increased cardiac output.[22,23] There is a continuing concern about the safety of NSBB use first raised from the window hypothesis. Recently, it has been reported that when using NSBB for >6 months in a patient with Child-Pugh class C, MELD 18 points or more, or ascites, OS is decreased from 15 months to 11 months.[24] Since β-adrenergic blockade could diminish cardiac output and possibly deteriorate hemodynamic circulation, the use of NSBB in patients with ascites may increase the incidence of AKI by about 3 times compared with patients without ascites.[25] In our study, the addition of NSBB to EVL did not give any further benefit in preventing variceal bleeding or reducing mortality rates.

Obviously, there are many confounding variables with which NSBB can interact in the process of preventing bleeding in patients with advanced liver cirrhosis and ascites. Actual drug use, changes in drug doses, other accompanying diseases, and differences in drug metabolism and drug susceptibility between each person will have some effects on benefits and harms that can be gained from the use of NSBB through various known or unknown routes. In the same vein, in addition to these unmeasurable biases, conflicting views of the effect of NSBB in decompensated cirrhosis would be closely related to the duration of drug use and observation period.

Regarding the dose of NSBB, 1 study has reported that propranolol does not affect survival if it is used at <160 mg even in decompensated state.[26] Similarly, in our study, no difference in mortality was observed according to dose of propranolol when propranolol was used at low doses. A recent study by Bang et al[26] in >3000 patients reported that the use of NSBB at doses >160 mg increased the mortality in patients with decompensated cirrhosis. Another study reported that long-term use of beta-blocker in cirrhotic patients for >6 months increased the mortality rate.[24,27] Thus, the use of high-dose, long-term nonselective beta-blockers may increase hemodynamic instability in patients with decompensated cirrhosis and increase the risk of various complications. In patients with difficult use of NSBB, scleroligation, as well as EVL, may be an effective alternative for patients with esophageal varices.[28] In patients with EV bleeding who did not respond to endoscopic treatment or vasoconstrictor administration, TIPS should be considered as rescue therapy.

The main limitation of our study arises from its retrospective observational design which entails biases of patient selection and recall. However, since liver cirrhosis patients with ascites have a high mortality and morbidity, it is very difficult to perform a controlled clinical study. We tried to minimize known and unknown confounding factors by PS matching. Also, medical records and lab data of the patients were carefully reviewed by 2 researchers, and in the case of disagreement, discussion was made to determine whether clinical outcome such as HRS or SBP was present. Second, direct comparison between NSBB and EVL is not possible in our study, because we did not have enough number of patients taking propranolol alone to include in the analysis.

Our results suggest that adding NSBB to EVL is not as effective as EVL alone because it may be associated with increased cirrhotic complication and mortality. On top of that, the addition of NSBB did not prevent further variceal bleeding, although it could reduce mortality from bleeding to some extent. However, such reduction was not statistically significant. Therefore, as a primary prevention of esophageal variceal bleeding in cirrhotic patients with significant ascites, EVL alone may be preferred over EVL plus NSBB combination treatment. For a more robust conclusion, a prospective randomized controlled study of these patients comparing 3 options (EVL only, NSBB only, combination therapy) will be needed in the future.

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