Comparison of Endoscopic Variceal Ligation and Nadolol Plus Isosorbide-5-mononitrate in the Prevention of First Variceal Bleeding in Cirrhotic Patients

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Background: Both drug therapy and banding ligation are widely used in the prevention of first variceal bleeding. This study compared the efficacy and safety of band ligation *vs.* combination of β-blocker and nitrate for the prevention of first bleeding in patients with cirrhosis and high-risk esophageal varices.

Methods: A total of 61 patients with cirrhosis with moderate or severe esophageal varices associated with red color signs but without history of variceal bleeding were randomized to band ligation (30 patients) or treatment with nadolol plus isosorbide-5-mononitrate (ISMN) (31 patients). In the ligation group, multiband ligator with 4 elastic bands was applied during each session. Ligation was repeated at intervals of 4 weeks until variceal obliteration was achieved. In the combination group, the dose of nadolol was sufficient to reduce the pulse rate by 25%. ISMN 1 tablet 20 mg qd or bid was administered.

Results: Both groups were similar in baseline characteristics. In the ligation group, variceal obliteration was achieved in 24 patients (80%), at a mean of 3.2 ± 0.9 ligation sessions and 11.7 ± 3.2 elastic bands. In the combination group, the mean daily doses of nadolol and ISMN administered were 40 ± 14 mg and 40 ± 12 mg, respectively. During a median follow-up of approximately 23 months, 5 patients (17%) in the ligation group and 8 patients (26%) in the combination group had upper-gastrointestinal bleeding ($p = 0.53$). Esophageal variceal bleeding occurred in 3 patients (10%) in the ligation group and 6 (19%) in the combination group ($p = 0.42$). By multivariate Cox analysis, presence of ascites was the only factor predictive of variceal bleeding. Minor complications were noted in 5 patients (17%) in the ligation group and 3 (10%) in the combination group ($p = 0.47$). Eight patients in the ligation group and 6 in the combination group died ($p = 0.49$). One (3%) patient in the ligation group and 3 (10%) in the combination group died of uncontrollable variceal bleeding.

Conclusion: Our preliminary results suggest that endoscopic variceal ligation is similar to the combination of nadolol plus ISMN with regard to effectiveness and safety in the prevention of first variceal bleeding in patients with cirrhosis. [*J Chin Med Assoc* 2006;69(10):453–460]

Key Words: banding ligation, isosorbide-5-mononitrate, nadolol, variceal bleeding

Introduction

Esophageal variceal hemorrhage is a catastrophic event of portal hypertension. Approximately 1-third of cirrhotic patients experience esophageal variceal bleeding, and the mortality rate associated with the first episode may reach 50%.[1] To prolong the survival of cirrhotic patients with esophageal varices, the first

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episode of variceal bleeding should be effectively prevented. In the past 2 decades, shunt operation and sclerotherapy have been tried with variable success. However, the resultant morbidities and mortalities have led to both modalities being abandoned.[1,2] On the other hand, endoscopic variceal ligation (EVL) has been well documented to be an effective method in the prevention of first variceal bleeding with a relatively low risk.[3–5] A meta-analysis showed that EVL was superior to β-blocker in reducing the occurrence of first variceal bleeding.[4] A combination of β-blocker and isosorbide-5-mononitrate (ISMN) has proven to be more effective than β-blocker alone in the prevention of secondary variceal bleeding.[6] Although combined treatment with nonselective β-blockers and nitrate has also been shown to be effective against first variceal bleeding,[7] to our knowledge, the comparison between EVL and combined drug therapy in the prevention of first variceal bleeding has never been reported. We, therefore, aimed to compare the efficacy and safety of band ligation with drug treatment using nadolol plus ISMN for the prophylactic prevention of first bleeding in cirrhotic patients with high-risk esophageal varices.

Methods

Patients

Between October 2002 and December 2004, patients presenting with chronic liver disease and esophageal varices were considered for enrollment in the trial. Inclusion criteria were: (1) portal hypertension caused by cirrhosis; (2) esophageal varices of moderate or severe grade, associated with any red color signs (red wale marking, cherry red spots, hematocystic spots); (3) no history of hemorrhage from esophageal varices; (4) no current treatment with β-blockers or nitrates. The diagnosis of cirrhosis was based on liver biopsy or clinical examination, biochemical tests and imaging studies. Exclusion criteria were: (1) age >75 years or <20 years; (2) presence of malignancy, uremia or other serious medical illness that could reduce life expectancy; (3) refractory ascites, hepatic encephalopathy or marked jaundice (serum bilirubin >10 mg/dL); (4) history of shunt operation, transjugular intrahepatic portosystemic stent shunt or endoscopic therapy (sclerotherapy or EVL); (5) contraindications to β-blockers or nitrates, e.g. asthma, chronic obstructive airway disease, diabetes mellitus with documented hypoglycemic episodes, congestive heart failure, peripheral vascular disease, hypotension (systolic blood pressure <90 mmHg) and bradycardia (pulse rate <60 beats/minute); (6) allergy to either trial medication or inability to cooperate.

Randomization

Patients eligible for the trial were randomized to undergo band ligation (EVL group) or treatment with nadolol plus ISMN (combination group). Randomization was by means of opaque, sealed envelopes numbered according to a table of random numbers. All the patients signed an informed consent and were followed-up regularly. The study protocol was approved by the ethics committee of our hospital.

Assessment

The diagnosis of cirrhosis was based on clinical and/or imaging findings. The severity of liver disease was assessed at presentation (Pugh modification of the Child classification).[8] Assessment of variceal size (degree) was based on the classification of Beppu et al.[9] Patients in both groups were advised to abstain from drinking alcohol.

Band ligation, nadolol and ISMN

Band ligation was applied after premedication with hyoscrine-N-butyl bromide (20 mg intramuscularly). A multiband ligator (Saeed Four-Shooter; Wilson-Cook Medical Inc., Winston-Salem, NC, USA) and a videoendoscope (XQ 230; Olympus Optical Co., Ltd., Tokyo, Japan) were utilized. Ligations were performed by 2 experienced endoscopists. During each session of treatment, 3–4 elastic bands were placed to ligate varices. The treatment interval was 4 weeks until all varices were obliterated or the residual varices were too small to be ligated. After variceal obliteration, patients in the EVL group underwent endoscopy every 3 months. EVL was repeated if varices recurred.

Among the patients in the combination group, 40 mg of nadolol once daily (E.R. Squibb & Sons, Inc., Princeton, NJ, USA) was given initially and then adjusted according to the dosage that reduced resting pulse rate by up to 25% or 55 beats/minute. Subsequently, 20 mg oral ISMN (F. Hoffmann-La Roche Ltd., Milan, Segrate, Italy) once per day was administered concomitantly. The dose was increased over a period of 1 week to 20 mg bid if tolerable. Compliance was assessed by reduction of pulse rate and/or by quantifying the number of tablets consumed, and inquiring about how often patients did not take the drugs. In case of side effects, nadolol was continued in patients who could not tolerate ISMN, and ISMN was continued in patients whose side effects were nadolol-related.

Patients in both groups were advised to undergo follow-up abdominal ultrasonography and to have

serum α-fetoprotein and biochemical tests of liver function at 3-month intervals.

Variceal bleeding and management

Patients suspected to have upper gastrointestinal bleeding underwent endoscopy within 12 hours of presentation. For patients with suspected esophageal variceal bleeding, supportive measures included blood transfusion, infusion of vasoconstrictor agents and administration of lactulose and prophylactic antibiotics. Esophageal variceal bleeding was defined as the appearance of hematemesis or melena, documentation of esophageal variceal bleeding at endoscopy, and a requirement for transfusion of >2 units of blood to maintain stable vital signs. EVL was performed within 24 hours of esophageal variceal bleeding in both groups. Elective EVL for prevention of recurrent bleeding was employed for those patients with failure of prophylaxis, if possible. Ligation sessions were repeated every 3–4 weeks until the varices were obliterated for both treatment groups.

Statistical analysis

Data were expressed as mean ± standard deviation. Quantitative variables were compared with Student's *t* test, and qualitative variables with χ^2 test and Fisher's exact test when appropriate. Kaplan–Meier estimation was applied to examine the time to first occurrence of variceal bleeding and the time to death. In the analysis of bleeding, patients were censored at death or at the end of follow-up. In the analysis of survival, patients were censored only at the end of follow-up. Log rank test was used to examine the variation of bleeding episodes and survival rate. Cox regression analysis was used to detect possible prognostic variables other than treatment modality on bleeding and survival rates. All hypothesis tests were conducted against a 2-sided alternative, where appropriate. A p value < 0.05 was considered to be significant. Analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). The possibility of hemorrhage from esophageal varices after prophylactic banding ligation varies from 0% to 15%.[10] The possibility of esophageal variceal bleeding after treatment with nadolol plus ISMN is about 12%.[6] We anticipated that if the possibility of first bleeding from esophageal varices was 12% in those receiving nadolol plus ISMN, which could be reduced to 6% in patients treated with EVL, with a 2-tailed test to achieve a statistical power of 80% and type I error of 5%, a sample size of 352 patients in each group would be required. However, it is impossible to enroll so many patients in a single center. Preliminary analysis of our results showed a similar trend. Thus, after 2 years of enrollment, we decided to terminate this study.

Results

General characteristics

During the study period, 70 patients were screened for possible inclusion in the trial. Of the 70 eligible patients, 9 were excluded due to hepatocellular carcinoma (2 patients), uremia (1), deep jaundice (2), refractory ascites (2), asthma (1) and hypotension (1).

A total of 61 patients were ultimately recruited: 30 were randomized to the EVL group and 31 to the combination treatment group with nadolol plus ISMN. The result was based on per protocol analysis (Figure 1). The 2 groups were comparable with regard to age, gender, variceal size and severity of liver disease (Table 1). There were no significant differences in both groups. The median duration of follow-up was 22.8 months (range, 4.6–41.7 months) for the EVL group and 23.8 months (range, 3.9–39.6 months) for the combination group. Three patients in the EVL group and 2 in the combination group continued to drink alcohol. No patients in either group were lost to follow-up.

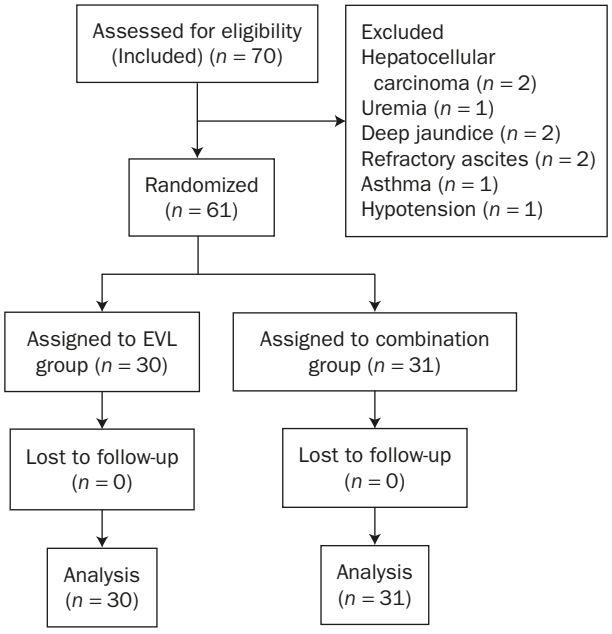

Figure 1. Clinical flow diagram of 77 cirrhotic patients assessed for eligibility. A total of 16 patients were excluded due to hepatocellular carcinoma, uremia, deep jaundice, refractory ascites, asthma and hypotension. A total of 61 patients were ultimately recruited, of which 30 were randomized to the EVL group and 31 to the combination group. No patients in either group were lost to follow-up. Therefore, all 61 patients were included in the analysis. EVL = endoscopic variceal ligation.

Table 1. Characteristics of the endoscopic variceal ligation (EVL) group ($n = 30$) and the combination group ($n = 31$) at study entry*

	EVL	Combination	*p*
Male/female	21/9	17/14	0.22
Age (yr)	60 ± 11	62 ± 11	0.92
Etiology of cirrhosis			
Alcoholism	5 (17)	6 (19)	1.00
Hepatitis B	10 (33)	9 (29)	0.72
Hepatitis C	11 (37)	14 (45)	0.50
HBV + HCV	2 (7)	1 (3)	0.61
Cryptogenic	2 (7)	1 (3)	0.61
Albumin (g/dL)	3.3 ± 0.6	3.3 ± 0.7	0.51
Bilirubin (mg/dL)	2.0 ± 1.7	2.0 ± 1.7	0.87
Ascites present	13 (43)	9 (29)	0.25
Prothrombin time (s)	2.4 ± 1.7	1.7 ± 2.1	0.15
Encephalopathy	0 (0)	1 (3)	1.00
Child–Pugh score	7.0 ± 1.7	7.2 ± 1.8	0.41
Child–Pugh class			
A	12 (40)	15 (48)	0.51
B	15 (50)	11 (35)	0.25
C	3 (10)	5 (16)	0.49
Variceal size			
F2	20 (67)	19 (61)	0.66
F3	10 (33)	12 (39)	0.66
Red color signs			
Mild	20 (67)	21 (68)	0.93
Moderate	9 (30)	10 (32)	0.85
Severe	1 (3)	0 (0)	0.49
Presence of gastric varices	10 (33)	10 (32)	0.93

**Data are expressed as mean ± standard deviation or n (%).*

Variceal obliteration was achieved in 24 patients (80%) in the EVL group. The mean number of treatment sessions required for successful obliteration was 3.2 ± 0.9. The causes of failure to achieve variceal obliteration included noncompliance (5 patients) and hepatic failure (1 patient). In the combination group, the median daily doses of nadolol and ISMN administered were 40 mg and 20 mg, respectively.

There were 10 patients each in both treatment groups with initial presence of gastric varices on enrollment. Newly developed gastric varices were observed in 2 patients (7%) in the EVL group but none in the combination group.

Upper gastrointestinal hemorrhage

Five patients (17%) in the EVL group and 8 (26%) in the combination group developed upper gastrointestinal

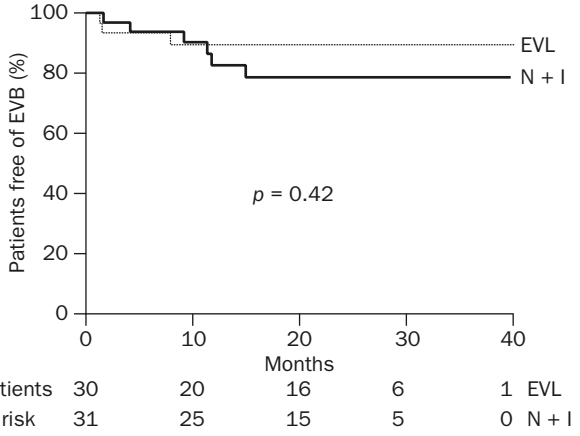

Figure 2. Kaplan–Meier probability estimates of being free from first bleeding from esophageal varices (EVB) in the 2 treatment groups. EVL = endoscopic variceal ligation; N + I = nadolol + isosorbide-5-mononitrate.

Table 2. Univariate analysis of risk factors for esophageal variceal bleeding

	Risk ratio	95% confidence interval	*p*
Gender	1.358	0.339, 5.436	0.664
Age	0.939	0.881, 1.000	0.051
Etiology of cirrhosis			
Alcoholism	4.341	1.163, 16.209	0.029
Hepatitis B	0.289	0.036, 2.311	0.242
Hepatitis C	0.604	0.150, 2.424	0.477
Albumin (g/dL)	0.904	0.339, 2.408	0.840
Bilirubin (mg/dL)	0.619	0.274, 1.396	0.248
Ascites present	4.243	1.050, 17.050	0.042*
Prothrombin time (s)	1.195	0.854, 1.674	0.299
Encephalopathy	0.723	0.887, 58.94	0.065
Treatment	1.757	0.439, 7.030	0.426

**In the definitive multivariate Cox proportional hazards regression analysis, only ascites present remained a significant risk factor.*

bleeding ($p=0.53$). Among these patients, 3 (10%) in the EVL group and 6 (19%) in the combination group bled from esophageal varices ($p=0.42$; Figure 2). Among those with bleeding in the EVL group, 2 patients bled from esophageal varices before variceal obliteration was achieved. One patient in the EVL group bled from esophageal varices once, as well as from gastric varices once. Bleeding from gastric varices was also encountered once in the combination group. Thus, gastroesophageal variceal bleeding occurred in 10% of the EVL group and 23% of the combination group ($p=0.29$). Two patients in the EVL group and 1 patient in the combination group bled from peptic ulcers. Univariate analysis showed that alcoholic etiology (risk ratio, 4.34; 95% CI, 1.16, 16.21; $p=0.029$) and presence of ascites (risk ratio, 4.24; 95% CI, 1.05, 17.05; $p=0.042$) were the variables significantly associated with an increased risk of variceal bleeding (Table 2). However, multivariate analysis showed that presence of ascites was the only significant prognostic predictor of first variceal bleeding (risk ratio, 4.24; 95% CI, 1.06, 17.05; $p=0.042$).

Complications

No serious adverse effect was found in either group. Minor complications were noted in 5 patients (17%) in the ligation group and 3 (10%) in the combination group ($p=0.47$). In the EVL group, 3 patients (10%) experienced transient dysphagia, 1 (3%) suffered from severe retrosternal pain that required pain control with analgesics and 1 (3%) developed esophageal ulcer after EVL. In the combination group, 2 patients complained of headache and 1 developed hypotension.

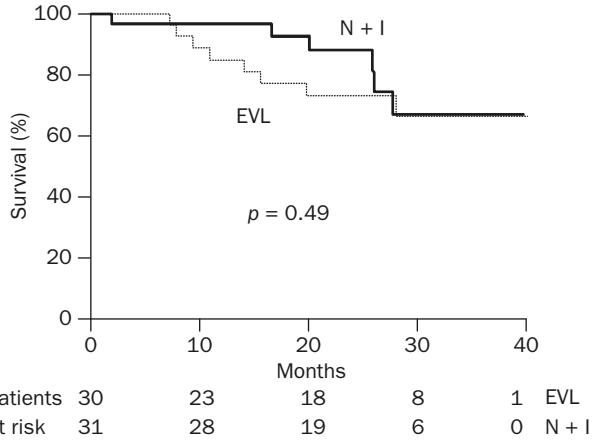

Figure 3. Kaplan–Meier probability estimates of survival in the 2 treatment groups. EVL = endoscopic variceal ligation; N + I = nadolol + isosorbide-5-mononitrate.

Mortality rates

There were 8 deaths in the EVL group and 6 deaths in the combination group ($p=0.49$; Figure 3). One patient in the EVL group and 3 in the combination group died of uncontrollable variceal bleeding (Table 3). Univariate analysis revealed that serum albumin, serum bilirubin, prothrombin time and presence of ascites were prognostic predictors of mortality, whereas multivariate analysis showed that prothrombin time was the only significant prognostic predictor of mortality (risk ratio, 1.69; 95% CI, 1.27, 2.23; $p<0.001$) (Table 4).

Discussion

Variceal bleeding is a dreadful complication of portal hypertension, which carries a high mortality rate.[1] It is one of those complications that, if prevented, can lead to improved survival. An analysis comparing propranolol with endoscopic injection sclerotherapy and shunt surgery suggested that β-blocker was the only cost-effective modality for primary prophylaxis.[11]

However, treatment with β-blocker does not result in obliteration of esophageal varices. Consequently, lifetime daily consumption of a β-blocker is necessary to maintain the effect.[12] Furthermore, the rate of non-response may be as high as 30%.[13] A significant number of patients (45%) reported side effects with β-blocker treatment, resulting in withdrawal from treatment in 30% of patients.[13] When propranolol is withdrawn, the risk of variceal hemorrhage returns to what would be expected in an untreated population. One study also reported that some patients might present with rebound bleeding upon abrupt cessation of treatment with β-blocker.[14] All of these situations are drawbacks of prophylactic β-blocker therapy against a first episode of variceal bleeding.

Because of an increase in mortality resulting from hepatic failure, nitrate monotherapy is not regarded as a useful regimen to prevent first variceal bleeding, despite a similar effectiveness to β-blocker monotherapy.[15] It has been demonstrated that combination therapy with a β-blocker and a nitrate could further reduce hepatic venous pressure and decrease the risk of primary variceal bleeding. Garcia-Pangan et al documented that hepatic venous pressure gradient (HVPG) decreased by more than 20% of baseline value in only 10% of patients receiving propranolol, but in 50% of patients receiving combined therapy.[16] Thus, from a clinical viewpoint, the efficacy and safety of a combination of β-blockers plus ISMN for primary prophylaxis is still controversial,[6,17,18] contrary to the secondary prophylaxis setting in which ISMN enhances the efficacy of a β-blocker.[19] A possible explanation for these results may depend on 2 facts: (1) most cirrhotic patients without episodes of variceal bleeding respond to β-blockers;[20] (2) the addition of ISMN reduces HVPG in non-responders to β-blocker, but not in responders.[21] However, the combination of β-blockers and ISMN has never been tried in primary prophylaxis in Chinese patients.

It is well accepted that EVL offers the same efficacy on varices as does endoscopic injection sclerotherapy

Table 3. Mortality in the endoscopic variceal ligation (EVL) group ($n = 30$) and combination group ($n = 31$)

	EVL *n* (%)	Combination *n* (%)
Variceal bleeding	1 (3.3)	3 (9.7)
Hepatic failure	3 (10.0)	2 (6.5)
Spontaneous bacterial peritonitis	1 (3.3)	1 (3.2)
Hepatorenal syndrome	2 (6.7)	0 (0)
Intracranial hemorrhage	1 (3.3)	0 (0)
Total	8 (26.7)	6 (19.4)

Table 4. Multivariate analysis of risk factors for mortality

	Risk ratio	95% confidence interval	*p*
Gender	0.815	0.281, 2.366	0.707
Age	0.967	0.925, 1.011	0.137
Etiology of cirrhosis			
Alcoholism	1.116	0.310, 4.011	0.867
Hepatitis B	1.145	0.357, 3.672	0.819
Hepatitis C	0.440	0.137, 1.410	0.167
Albumin (g/dL)	0.356	0.133, 0.955	0.040
Bilirubin (mg/dL)	1.249	1.042, 1.497	0.016
Ascites present	2.992	1.036, 8.642	0.043
Prothrombin time (s)	1.686	1.272, 2.234	< 0.001*
Encephalopathy	0.048	0.000, 1.293	0.759
Treatment	0.689	0.239, 1.990	0.492

**In the definitive multivariate Cox proportional hazards regression analysis, only the prothrombin time remained a significant risk factor.*

but with fewer adverse effects and, thus, is the more favored endoscopic approach to prevent first variceal bleeding compared with sclerotherapy.[22] A meta-analysis of EVL for primary prophylaxis of esophageal variceal bleeding demonstrated that EVL achieved a lower risk for first variceal bleeding when compared with β-blocker (relative risk, 0.48).[4] Up to now, a large number of studies have investigated the roles of sclerotherapy, β-blocker and EVL in preventing first variceal bleeding.[2,6] However, there is still no controlled study to compare EVL with a combination of nitrate plus β-blocker for prevention of first variceal bleeding. Hence, we carried out this study to investigate whether nadolol plus ISMN compared to EVL made a difference in the prevention of first variceal bleeding in patients with cirrhosis.

The present trial compared EVL with nadolol plus ISMN for prevention of first variceal bleeding. The upper gastrointestinal bleeding rate was 17% in the EVL group and 26% in the combination group ($p = 0.53$), a difference that was not statistically significant. Our esophageal variceal bleeding rate was 10% in the EVL group and 19% in the combination group ($p = 0.47$). Our results were comparable with those of previous trials that found variceal bleeding rates of 9% to 19% in patients receiving prophylactic EVL,[8,9,23–25] but slightly higher than the bleeding rate of 7.5% in patients treated with nadolol plus ISMN.[10] Because of the small difference in reducing variceal bleeding rate, it would require a large sample size to reach a statistically significant difference between EVL and combination drug therapy. EVL treatment intervals were 4 weeks instead of weekly. Thus, the length of time required to obliterate esophageal varices was slightly longer in the present trial. The current trial had fewer esophageal ulcers as compared with prior studies. This is in disagreement with a past study by Sarin et al,[24] which reported that esophageal ulcers were observed in 80% of patients. On the other hand, the current trial included cirrhotic patients with gastric varices. Only 1 patient in the combination group bled from gastric varices. To our knowledge, the presence of gastric varices is not an absolute contraindication to EVL. Therefore, cirrhotic patients with esophageal varix with/without gastric varix were analyzed for this study.

In combined medical therapy, the daily doses of nadolol and ISMN to prevent first esophageal variceal bleeding were lower in our patients compared to other trials. Borroni et al reported that their final daily dose of nadolol was 68 ± 7 mg and ISMN was given at the initial dose of 20 mg and doubled every 3–4 days until 40 mg bid.[26] A Spanish study used a mean dose of 95 ± 56 mg/day for nadolol and the dose of ISMN was increased to 40 mg bid.[27] We presume that the varying tolerable dose of ISMN among the different study groups may be ascribed to ethnic differences.

Incidences of aspiration pneumonia and esophageal bleeding after prophylactic EVL have been reported.[3] Fortunately, no serious complication was found in the current trial. Minor complications occurred with similar frequency in both groups.

There were no significant differences between the 2 treatment groups with regard to survival rates. Patients who underwent EVL had a lower risk of dying from uncontrollable variceal bleeding than those who received combination therapy, but the difference was not significant. Our study results are in agreement with those of a meta-analysis of primary prophylaxis, which showed that survival was similar between those treated with EVL and those treated with drug therapy.[4,10]

Our preliminary results suggest that EVL has similar effectiveness and safety to the combination of nadolol plus ISMN in the prophylaxis against first variceal bleeding. However, a larger, randomized controlled trial is needed.

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