Emergency Endoscopic Variceal Ligation versus Somatostatin for Acute Esophageal Variceal Bleeding

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Background: Endoscopic variceal ligation and somatostatin are widely used for treating acute esophageal variceal bleeding. This study compared the efficacy, safety, and survival of both therapies.

Methods: Acute esophageal variceal bleeding patients were randomized to undergo emergency ligation or receive a bolus of 250 μg somatostatin plus infusion at 250 μg/hour for 48 hours and undergo ligation subsequently.

Results: Three (4.8%) of 62 patients in the ligation group and 20 (31.7%) of 63 patients in the somatostatin group encountered treatment failure ($p = 0.0001$). Transfusion requirements were 4.7 ± 3.2 units in the ligation group and 6.9 ± 7.3 units in the somatostatin group ($p = 0.03$). Hospital stay was 7.7 ± 4.0 days in the ligation group and 10.2 ± 9.9 days in the somatostatin group ($p = 0.07$). Adverse effects occurred in the ligation group (20 episodes) and the somatostatin group (27 episodes) ($p = 0.2$). The 42-day mortality rates were 5 patients (8.1%) in the ligation group and 3 patients (4.8%) in the somatostatin group ($p = 0.5$).

Conclusion: Emergency ligation was superior to somatostatin in treating acute esophageal variceal bleeding, with fewer requirements of transfusion and a tendency toward shorter hospital stay. The adverse effects and 42-day mortality rates were similar between both treatments. [*J Chin Med Assoc* 2006;69(2):60–67]

Key Words: cirrhosis, ligation, somatostatin, variceal bleeding

Introduction

Acute esophageal variceal bleeding (EVB) is a severe complication of portal hypertension, with a mortality rate ranging from 30% to 50%.[1] A large number of studies have been published on the management of acute EVB. Vasoactive drugs are often considered as the first-line therapy for acute EVB because they are effective and easy to use. Among the vasoactive drugs, somatostatin (SMT) produces a significant and sustained decrease in the hepatic venous pressure gradient.[2] It could control acute EVB in 60–80% of cases.[3]

The optimal timing of endoscopic treatment for acute EVB remains undetermined.[4] It has been suggested that endoscopic therapies should be the first choice of treatment for acute EVB and that success in control of bleeding could be achieved in 80–90% of cases.[4,5] Several studies have shown emergency sclerotherapy and vasoactive drugs to have similar efficacy of hemostasis.[6–8] However, a recent meta-analysis found that vasoactive drugs were as effective as emergency sclerotherapy, but sclerotherapy carried an increased risk of adverse effects.[9] It was concluded that the available evidence did not support emergency sclerotherapy as first-line treatment when compared with vasoactive drugs, and endoscopic treatment might be limited to pharmacologic treatment failure.

Endoscopic variceal ligation (EVL) and sclerotherapy are both effective endoscopic therapies

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for acute EVB.[10] EVL is replacing sclerotherapy because it has fewer complications than sclerotherapy and decreases the early rebleeding rate.[5,11,12] Our previous trial found that EVL was superior to sclerotherapy in the control of active EVB.[13] Emergency EVL was also recommended in the UK guidelines as the treatment of choice for acute EVB,[14] whereas some experts still favor using vasoactive drugs as first-line therapy.

Although emergency EVL and SMT are often used in the treatment of acute EVB, no study has compared the efficacy of these 2 therapies.[3,9,10] We conducted this trial to test the hypothesis that emergency EVL is better at controlling acute EVB than SMT. We also compared the adverse effects and survival of both treatments.

Methods

Patients presenting with acute EVB were considered for enrollment in the study. The inclusion criteria were the following: (1) a history of cirrhosis; (2) acute EVB presenting with hematemesis, melena, or both; (3) hospital arrival within 12 hours after onset of the symptoms; (4) no use of vasoactive drugs or endoscopic therapy before referral to our hospital; and (5) age between 20 and 75 years. Patients with the following conditions were excluded: (1) a Child-Pugh score greater than 12 points; (2) hepatorenal syndrome or uremia; (3) comatous status; (4) hepatocellular carcinoma or other malignancy; (5) portal vein thrombosis; (6) sclerotherapy or banding ligation within 3 months; (7) use of β-blocker within 1 week; (8) previous surgical or transjugular intrahepatic portosystemic stent shunt; and (9) refusal to participate in the study. After resuscitation and adequate transfusion, emergency endoscopy was performed within 12 hours after the patient's arrival at the hospital. Eligible patients were randomized into the emergency EVL group or SMT group. The endpoint of this study was failure to control acute EVB within 48 hours.

Randomization of patients

Patients were immediately randomized to receive emergency EVL or SMT infusion during the emergency endoscopy. A statistician created sequentially numbered opaque and sealed envelopes containing a digit (1 for the emergency EVL group and 2 for the SMT group) derived from computer-generated random numbers. The investigators opened the envelopes and assigned the patients to the designated groups. This protocol was approved by the Medical Ethics Committee of the hospital. All patients and their next of kin understood the treatment protocol and gave their consent before the emergency endoscopy.

Emergency EVL

Patients randomized to the emergency EVL group underwent EVL immediately after initial endoscopic examination. Emergency EVL was performed by 3 experienced endoscopists who had performed at least 200 cases of EVL prior to this study. The ligation procedure included the use of an overtube, a pneumoactive ligation device (Sumitomo Bakelite Co., Ltd, Tokyo, Japan), and an Olympus XQ-230 videoendoscope (Olympus Optical Co., Ltd, Tokyo, Japan). The varices were ligated with 4–8 rubber bands from the gastroesophageal junction and the stigmata of recent bleeding, such as a white nipple sign or active bleeding site, if present. Patients were allowed to start a liquid diet for 3 days and normal or low-salt diet subsequently if they did not encounter treatment failure within 48 hours.

SMT infusion

Patients randomized to the SMT group received an initial bolus of 250 μg SMT during the emergency endoscopy when the diagnosis of acute EVB was established. A continuous infusion of SMT maintained at 250 μg/hour was used for the next 48 hours. A nasogastric tube was inserted soon after endoscopic examination. Gastric lavage was performed at 4-hour intervals to monitor the efficacy of hemostasis. If the aspirated content became clear persistently for 24 hours, the nasogastric tube was removed. If acute EVB was controlled, patients underwent elective EVL at 48 hours after randomization. Patients were then allowed to take a liquid diet for 3 days and normal or low-salt diet subsequently. If a bolus of SMT failed to control bleeding in patients with active bleeding during emergency endoscopy, alternative treatments, including a balloon tamponade using a Minnesota tube, EVL, and transjugular intrahepatic portosystemic stent shunt with or without the combination of SMT infusion, were offered to the patients according to their choice or that of their next of kin.

General care of patients

Patients were resuscitated and transfused with packed red cells, whole blood, and fresh frozen plasma during the study period, aiming at maintaining hematocrit between 27% and 30%. The pulse rate, blood pressure, and urine output were closely monitored. Patients were given oral lactulose for 2 weeks to prevent hepatic encephalopathy. Patients also received oral sucralfate after EVL to enhance the healing of ligation-induced

esophageal ulcers. Prophylactic intravenous cefazolin (1 g every 6 hours) was administered for 3 days after randomization to prevent possible concomitant infection and this prescription was changed according to the results of bacterial cultures if frank infection occurred. If emergency EVL or SMT failed to control acute EVB, alternative treatments, including a balloon tamponade using a Minnesota tube, repeated EVL, and transjugular intrahepatic portosystemic stent shunt with or without the combination of SMT infusion, were offered to the patients. Adverse effects associated with emergency EVL and SMT were prospectively recorded and categorized into major or minor adverse effects. All patients who survived the acute EVB episode were enrolled into an ongoing trial comparing oral nadolol plus isosorbide-5-mononitrate and repeated sessions of EVL to prevent recurrent variceal bleeding and were discharged from the hospital 2 days later.

Definitions

Acute EVB was defined as bleeding from an esophageal varix at the time of endoscopy or the presence of large varices with blood in the stomach and no other recognizable cause of bleeding.[14] The severity of esophageal varices was graded based on Beppu et al's[15] system. Active bleeding was defined as oozing or spurting seen on endoscopy. Hypovolemic shock was defined as a pulse rate higher than 120 beats per minute or systolic blood pressure lower than 80 mmHg. The definition of treatment failure of acute EVB followed the Baveno II consensus.[16] Successful treatment was defined as absence of treatment failure and survival during the 48-hour study period. Any new hematemesis or melena after 48 hours from randomization was defined as the first rebleeding episode.

Sample size calculation

The expected efficacy of SMT infusion in controlling acute EVB was approximately 70%.[6] The corresponding figure for emergency EVL was approximately 90% according to our experience.[13] The sample size needed to detect significant differences of hemostatic efficacy was calculated as 62 patients in each group using a 2-sided test with 80% power at a significance level of 5%.

Statistical analysis

Clinical data were reported as means ± SD. Continuous variables of both groups were compared with the independent Student *t*-test or the nonparametric Mann-Whitney rank sum test for unpaired data. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Stepwise Cox regression analysis was used to examine the independent predictors for treatment failure and 42-day mortality. The actuarial survival curves of both groups were constructed using the Kaplan-Meier method and compared with a log-rank test. The SPSS statistical package (SPSS 10.0; SPSS, Inc., Chicago, IL, USA) was used. A p value of less than 0.05 was considered statistically significant.

Results

A total of 296 patients with acute EVB were recruited from August 2000 through May 2004. One hundred and seventy-one patients were excluded because of banding ligation within 3 months (38 patients), use of β-blocker within 1 week prior to the EVB episode (37 patients), a Child-Pugh score greater than 12 points (20 patients), uremia (5 patients), hepatocellular carcinoma (57 patients), cholangiocarcinoma (2 patients), breast cancer (1 patient), colon cancer (2 patients), pancreatic cancer (1 patient), laryngeal cancer (1 patient), previous transjugular intrahepatic portosystemic stent shunt (2 patients), and refusal to participate in the study (5 patients) (Figure 1). The eligible 125 patients were entered into the study and randomized to the emergency EVL group (62 patients) and SMT group (63 patients). The demographic, clinical, and laboratory features of the included patients are presented in Table 1. The age, gender, etiologies and severity of cirrhosis, the severity of esophageal varices, numbers of active bleeders, concomitant gastric varices, a history of previous variceal hemorrhage, hematocrit, serum glucose level, renal function, transfusion before randomization, and numbers of patients with infection were not significantly different between the 2 groups. The time elapsed from admission to diagnostic endoscopy was 6.9 ± 4.3 hours in the emergency EVL group and 7.0 ± 4.4 hours in the SMT group (p = 0.9).

Treatment failure

Of the 62 patients undergoing emergency EVL, 3 (4.8%) experienced treatment failure (Table 2). Two patients received repeated emergency EVL and 1 received a balloon tamponade with subsequent EVL for treatment failure. Of the 63 SMT group patients, 20 (31.7%) encountered treatment failure. For the treatment failure patients, 13 received emergency EVL and 7 received a balloon tamponade and subsequent EVL. Patients in the SMT group had a significantly higher proportion of treatment failure than patients in the emergency EVL group (p = 0.0001, Figure 2). Of the subgroup of patients who

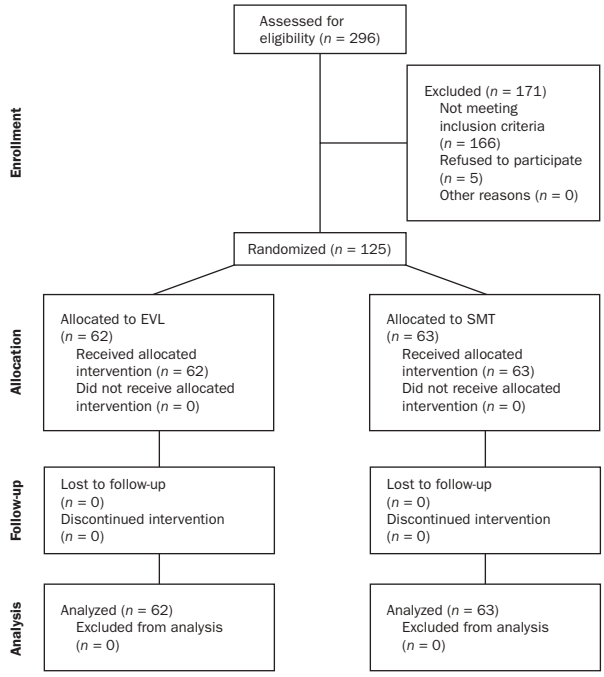

Figure 1. The CONSORT diagram showing the flow of participants through each stage of this study.

had active bleeding at the initial endoscopy, patients in the SMT group had a higher rate of treatment failure than emergency EVL group patients (69.2% vs 11.8%, $p = 0.002$). Of the subgroup of nonactive-bleeding patients at the initial endoscopy, the proportion of treatment failure was also higher in the SMT group than in the emergency EVL group (22.0% vs 2.2%, $p = 0.004$). Univariate analysis by Cox regression showed that SMT infusion (relative risk, 6.4; 95% confidence interval [CI], 1.9–21.9; $p = 0.003$) and active bleeding at initial endoscopy (relative risk, 2.8; 95% CI, 1.1–6.9; $p = 0.03$) were associated with treatment failure. SMT infusion (relative risk, 6.7; 95% CI, 1.9–23.6; $p = 0.003$) and active bleeding (relative risk, 3.1; 95% CI, 1.2–8.0; $p = 0.02$) were found to be independent predisposing factors of treatment failure by multivariate analysis using stepwise Cox regression.

Emergency EVL group patients had significantly fewer requirements for transfusion during the admission period than SMT group patients (4.7 ± 3.2 vs 6.9 ± 7.3 units, $p = 0.03$; Table 2). Patients in the emergency EVL group also had a trend toward shorter hospital stay when compared with patients in the SMT group (7.7 ± 4.0 vs 10.2 ± 9.9 days, $p = 0.07$).

Table 1. Clinical characteristics of patients randomized to receive emergency endoscopic variceal ligation (EVL) and somatostatin (SMT) infusion

	EVL group (n = 62)	SMT group (n = 63)	p value
Age, yr	54.5 ± 12.8	51.8 ± 15.2	0.3
Sex, male/female	43/19	52/11	0.1
Etiology of cirrhosis			
HBV/HCV/alcohol/other	11/19/24/8	15/14/29/5	0.5
Hematocrit, %	25.6 ± 7.1	26.3 ± 7.0	0.6
Serum albumin, g/dL	2.9 ± 0.5	3.0 ± 0.5	0.5
Serum bilirubin, mg/dL	3.0 ± 4.1	3.0 ± 2.8	0.9
Ascites	34	33	0.8
Prothrombin time-prolonged, sec	2.3 ± 2.4	2.3 ± 2.3	0.9
Encephalopathy	15	19	0.5
Child-Pugh class, A/B/C	13/31/18	18/27/18	0.6
Child-Pugh score	8.3 ± 2.0	8.3 ± 2.3	0.9
Serum creatinine, mg/dL	1.1 ± 0.7	1.2 ± 0.6	0.9
Serum glucose, mg/dL	171.2 ± 100.7	211.1 ± 132.6	0.06
Diabetes	20	22	0.8
Hypovolemic shock	8	13	0.3
Active bleeding at endoscopy	17	13	0.4
Variceal size, F1/F2/F3	5/38/19	2/41/20	0.5
Presence of gastric varices	22	21	0.8
Transfusion before randomization, units	4.1 ± 2.7	4.6 ± 3.7	0.4
Infection	6	7	0.7
Previous episode of variceal bleeding	14	15	0.9

HBV = viral hepatitis B; HCV = viral hepatitis C.

Table 2. Results of treatment

	EVL group (n = 62)	SMT group (n = 63)	p value
Treatment failure			
Overall	3	20	0.0001
Active-bleeding patients	2	9	0.002
Nonactive-bleeding patients	1	11	0.004
Total transfusion, units	4.7 ± 3.2	6.9 ± 7.3	0.03
Serum glucose at 48 hours, mg/dL	156.9 ± 88.2	179.3 ± 103.5	0.4
Hospital stay, d	7.7 ± 4.0	10.2 ± 9.9	0.07
Rebleeding	4	3	0.7

EVL = endoscopic variceal ligation; SMT = somatostatin.

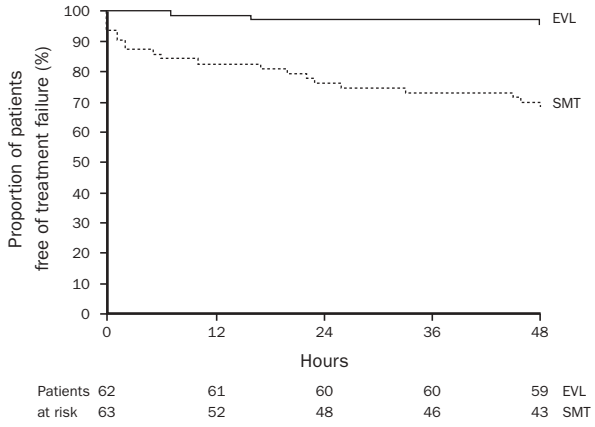

Figure 2. Cumulative probability of patients remaining free of treatment failure during 48 hours. Patients undergoing emergency endoscopic variceal ligation had a significantly higher proportion free of treatment failure at 48 hours than patients receiving somatostatin infusion (95.2% vs 68.3%, p = 0.0001). EVL = endoscopic variceal ligation; SMT = somatostatin.

Table 3. Adverse effects of patients receiving emergency endoscopic variceal ligation (EVL) and somatostatin (SMT) infusion during 48 hours

	EVL group	SMT group
Total episodes	20	27
Mild adverse effects	18	23
Chest pain	7	0
Odynophagia	5	1
Epigastralgia	1	2
Abdominal fullness	2	0
Abdominal cramps	1	3
Nausea and vomiting	2	5
Hyperglycemia	–	12
Severe adverse effects	2	4
Aspiration pneumonia	1	2
Sepsis	1	1
Hyperosmolar nonketotic coma	–	1

Rebleeding

After control of acute EVB, 37 patients in the emergency EVL group underwent repeated EVL and the other 25 patients received nadolol plus isosorbide-5-mononitrate to prevent recurrent EVB. Four patients (6.4%) experienced rebleeding within 42 days, which was controlled by EVL. Of the patients in the SMT group, 35 underwent repeated EVL and 28 received nadolol plus isosorbide-5-mononitrate to prevent rebleeding. Seven patients (11.1%) experienced rebleeding within 42 days, which was controlled by EVL, except for 1 patient who underwent transjugular intrahepatic portosystemic stent shunt creation because of uncontrolled rebleeding. There was no significant difference in the modalities used to prevent rebleeding and the rebleeding episodes between the emergency EVL group and the SMT group.

Adverse effects

In total, 20 episodes of adverse effects were found in the emergency EVL group within 48 hours (Table 3). Chest pain and odynophagia were the most common mild adverse effects. Two episodes of severe adverse effects, including aspiration pneumonia and sepsis, were found in each of the patient groups. Patients in the SMT group had 27 episodes of adverse effects. Hyperglycemia and nausea accounted for most of the mild adverse effects. Four episodes of severe adverse effects, including aspiration pneumonia (2 episodes), sepsis (1 episode), and hyperosmolar nonketotic coma (1 episode), were found. The total incidences of adverse effects were not significantly different between the 2 groups (p = 0.2).

Survival

The 42-day mortality rates were 5 patients (8.1%) in the emergency EVL group and 3 patients (4.8%) in

the SMT group (p = 0.5, Figure 3). No mortality within 48 hours was found in either of the groups. The Child-Pugh scores of the mortality patients in the emergency EVL group were 11 points in 4 patients and 12 points in 1 patient. The Child-Pugh scores of the mortality patients in the SMT group were 11 points in 1 patient and 12 points in 2 patients. The causes of mortality are shown in Table 4. Only 1 patient in the emergency EVL group died of uncontrolled variceal bleeding, at day 30. Univariate analysis by Cox regression showed that active bleeders at initial endoscopy (relative risk, 5.5; 95% CI, 1.3–23.2; p = 0.02) and Child-Pugh score (relative risk, 2.2; 95% CI, 1.5–3.1; $p < 0.001$) were predictors for 42-day mortality. Multivariate analysis by stepwise Cox regression found that Child-Pugh score was the only independent predictor for 42-day mortality (relative risk, 2.2; 95% CI, 1.5–3.1; $p < 0.001$).

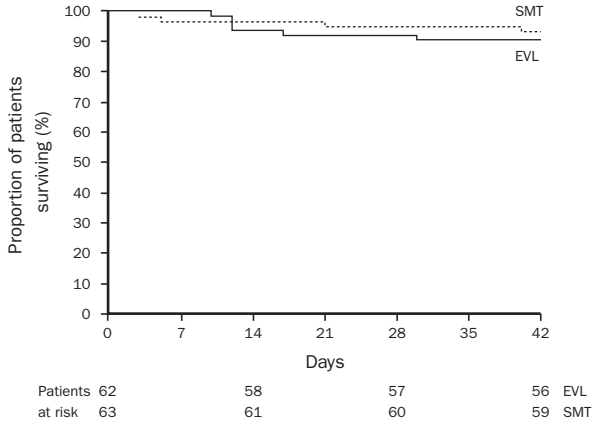

Figure 3. Cumulative survival of patients undergoing emergency endoscopic variceal ligation and receiving somatostatin infusion. There was no significant difference in survival between the groups (p = 0.5). EVL = endoscopic variceal ligation; SMT = somatostatin.

Table 4. Mortality of patients undergoing emergency endoscopic variceal ligation (EVL) and somatostatin (SMT) infusion for acute esophageal variceal bleeding

	EVL group	SMT group
Mortality within 42 days	5	3
Causes of mortality		
Variceal bleeding	1	0
Liver failure	2	0
Aspiration pneumonia	1	2
Sepsis	1	1

Discussion

The present study confirmed our hypothesis that emergency EVL had an advantage over SMT in the control of acute EVB, both in the active bleeders and the nonactive bleeders. Patients in the emergency EVL group had fewer requirements for transfusion than patients in the SMT group because of fewer episodes of treatment failure. Additionally, patients undergoing emergency EVL had a trend toward shorter hospital stay compared with patients receiving SMT infusion because EVL was used early.

The high success rate of emergency EVL in controlling acute EVB was consistent with previous trials.[11–13] Two possibilities may account for the higher hemostasis rate by emergency EVL than SMT. First, hemostasis by EVL is achieved by mechanical strangulation of the varix at or near the bleeding site and probably results in a more sustained efficacy of hemostasis. On the contrary, SMT decreases portal pressure and achieves hemostasis by inhibiting glucagon and gastrointestinal vasodilatory peptides.[3] A decrease of hepatic venous pressure gradient greater than 10% from the baseline was found in only 60% of bleeding patients using SMT.[2] The difference in treatment failure rates between SMT and emergency EVL in this trial was more marked for active-bleeding patients (69.2% vs 11.8%). Second, emergency EVL offers a definitive treatment in addition to achieving initial hemostasis, but the hemostasis by SMT is usually not durable and patients require subsequent endoscopic therapies or portal hypotensive drugs. It was noteworthy that a nasogastric tube was used in the SMT group after emergency endoscopy but not in the EVL group because insertion of a nasogastric tube was inappropriate in the patients who had just received EVL. The absence of the use of a nasogastric tube in the EVL group may lead to a potential underestimation of the rebleeding rate. Besides, SMT was started when acute EVB was found during an emergency endoscopy in the SMT group patients. It was possible that the time lag of drug therapy decreased the efficacy of SMT.

The episodes of adverse effects were comparable between the emergency EVL group and the SMT group in this trial. Chest pain and hyperglycemia were the most common mild adverse effects of emergency EVL and SMT infusion, respectively. Few severe adverse effects were associated with both therapies. Interestingly, sepsis and hyperosmolar nonketotic coma occurred in a diabetic patient in the SMT group. Whether SMT was involved in the development of hyperosmolar nonketotic coma in this case was not

known. However, close monitoring of the serum glucose level during the administration of SMT, especially in patients with diabetes, may be necessary, because bacterial infection is frequently seen in cirrhotic patients with gastrointestinal bleeding.[17]

The advancement of therapy for acute EVB has improved the survival of cirrhotic patients.[18,19] The 42-day mortality rate was recently estimated to be about 20%.[20] The 42-day mortality rates of our patients (8.1% for the emergency EVL group and 4.8% for the SMT group) were comparable with those of a study investigating sclerotherapy and SMT (8.9% for each arm).[7] Although more patients in the SMT group encountered treatment failure, no patient died of variceal bleeding because of effective rescue EVL or a balloon tamponade with subsequent EVL. In fact, we found that a high Child-Pugh score was the only independent predictor for mortality. The low mortality rates in our patients may be due to the enrollment of patients with a Child-Pugh score equal to or less than 12 points, the exclusion of patients with hepatocellular carcinoma (a confounding factor for controlling acute EVB), and the routine use of antibiotics that improve survival in an acute EVB episode.[17] Nevertheless, it should be recognized that the 42-day mortality rate, as well as the 42-day rebleeding rate, was not the primary endpoint of this study, although the later interventions in the prevention of rebleeding were not significantly different in either group.

Although the current study showed that early EVL was beneficial for variceal bleeding patients, the high efficacy of emergency EVL does not necessarily discard the use of vasoactive drugs. Early administration of vasoactive drugs may improve the efficacy of therapeutic endoscopy and reduce the rate of treatment failure.[21] It was, therefore, suggested in Baveno III that vasoactive drugs should be started as soon as possible before diagnostic endoscopy.[22] Vasoactive drugs were not used prior to diagnostic endoscopy in this trial because the study was designed just before the consensus was reached, and this may raise critical concerns. Nevertheless, all the patients were properly managed before randomization and effective treatments were used immediately once the diagnosis of acute EVB was established. Alternative therapies were offered to the SMT group patients if a bolus of SMT failed to control active bleeding. A reasonable strategy is to start vasoactive drugs at admission with associated endoscopic therapy at the time of diagnostic endoscopy.[20,23] However, EVL combined with a vasoactive drug does not result in a better survival than EVL alone, although the combination therapy is more effective than EVL in the control of acute EVB.[24,25] More adverse effects might be expected with the combination therapy than vasoactive drugs or endoscopic treatment alone.[9] Future randomized controlled trials would be necessary to compare vasoactive drugs and emergency EVL with vasoactive drugs to determine the optimal timing of EVL.

In conclusion, emergency EVL and SMT were both effective and safe treatments for acute EVB. Emergency EVL was superior to SMT in terms of controlling acute EVB, reducing the requirements for transfusion, and shortening the hospital stay. These findings suggest that early EVL for patients with acute EVB is encouraged if endoscopists experienced in EVL are available.

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