

No Mortality Difference Following Treatment with Terlipressin or Somatostatin in Cirrhotic Patients with Gastric Variceal Hemorrhage

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ABSTRACT

Background/Aims: The aim of this study was to compare the efficacy of terlipressin versus somatostatin as adjuvants to endoscopic treatment in cirrhotic patients with gastric variceal bleeding. **Patients and Methods:** The National Health Insurance Database, derived from the Taiwan National Health Insurance Program, was used to enroll patients who were discharged with International Classification of Diseases, 9th Revision, Clinical Modification diagnoses of cirrhosis and who underwent gastric variceal sclerotherapy for gastric variceal bleeding between January 1, 2007, and December 31, 2007. We observed treatment outcomes and identified clinical factors associated with mortality. **Results:** In total, we enrolled 311 cirrhosis patients who underwent sclerotherapy for active gastric variceal bleeding. Among them, 218 patients received terlipressin, and 93 patients received somatostatin. The overall 30 day mortality rate was 13.2% (41/311). A total of 78 (25.1%) patients underwent second-look endoscopy, but only 12 (7%) needed a second course of gastric variceal sclerotherapy. The overall 30-day mortality rates for patients treated with terlipressin and somatostatin were 13.3% and 12.9%, respectively, showing no statistically significant differences between outcomes in the two treatment groups ($P = 0.672$). The risk of 30-day mortality was significantly higher in patients with hepatocellular carcinoma (HR: 3.257, 95% CI: 1.640-6.469, $P = 0.001$), acute renal failure (HR: 6.261, 95% CI: 2.376-16.499, $P < 0.001$), or hepatic encephalopathy (HR: 3.091, 95% CI: 1.430-6.680, $P = 0.004$). **Conclusions:** Mortality rates did not differ significantly between cirrhosis patients with acute gastric variceal bleeding who received somatostatin or terlipressin as adjuvants to endoscopy.

Key Words: Gastric variceal bleeding, somatostatin, terlipressin

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Gastroesophageal varices are a common clinical presentation in patients with portal hypertension, and variceal bleeding is a frequent, lethal complication of cirrhosis.^[1] Gastric varices (GVs) are less prevalent, and are associated with a lower bleeding risk than esophageal varices.^[1-4] However, the severity of bleeding and the associated mortality rate are significantly higher in patients who present with GV's.^[1,2]

Tissue adhesives are the endoscopic treatment of choice for bleeding from GV's, and are recommended by the Baveno V, National Institute of Health and Care Excellence (NICE), American Association of the Study of Liver Diseases (AASLD), and American Society for Gastrointestinal Endoscopy (ASGE) guidelines.^[5-8] If variceal hemorrhage is confirmed, pharmacological therapy should be continued for 3-5 days after endoscopy. Three vasoactive drugs (somatostatin, terlipressin, and octreotide) play a role in the control of variceal bleeding by reducing portal blood flow and portal pressure. Studies have proved the efficacy

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of vasoactive medications in patients who experience acute variceal bleeding.^[9,10] The choice of vasoactive drug in patients with acute varices bleeding should be based on local resources.^[11] There is evidence that clinicians have no preference when choosing between these vasoactive drugs because they seem to be equally effective,^[9,12,13] although some reports^[10,14] have suggested terlipressin as the first choice because it is the only drug found to improve survival in a meta-analysis.^[10] Most research has compared the effect of vasoactive agents in enrolled populations with active esophageal variceal bleeding.^[12,13,15,16] To date, no study has investigated the use of various vasoactive drugs specifically in controlling GV bleeding.

To identify the effects of vasoactive agents on GV bleeding-related mortality in patients with cirrhosis, we used Taiwan's nationwide population-based data set to enroll patients with cirrhosis. The choice of vasoactive agents in this country includes somatostatin and terlipressin, and octreotide was therefore excluded from our study. We compared the efficacy of terlipressin versus somatostatin as adjuvants to endoscopic treatment in patients with GV bleeding in cirrhosis. We also tried to identify clinical factors associated with mortality following endoscopic GV sclerotherapy.

PATIENTS AND METHODS

Database

In 1995, Taiwan started the National Health Insurance (NHI) program. Currently, the NHI Bureau (NHIB) covers more than 95% of the Taiwanese population. For medical payment, all medical records from all contracted medical institutions are required by the NHIB. The NHI Research Database (NHIRD) is maintained by the NHIB and the National Health Research Institute (NHRI). This secondary, de-identified data set includes all diagnostic coding information of hospitalized patients in Taiwan. All investigators using this database are required to undergo evaluation by the NHRI. This study was approved by the NHRI (application and agreement number 101516), and the privacy of patients and health care providers was protected.

This study was initiated with approval of the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Chiayi, Taiwan (IRB B1010410). The review board waived the requirement for written informed consent from all patients because all identifying personal information was removed from the secondary files before analysis.

Study sample

We enrolled patients who were discharged with International Classification of Diseases, 9th Revision, Clinical Modification

(ICD-9-CM) diagnoses of cirrhosis (ICD-9-CM code 571.5 or 571.2) and who received GV sclerotherapy (GVS) for GV bleeding between January 1, 2007, and December 31, 2007. In cases of multiple hospitalizations, only the first episode was included. In total, 311 patients with cirrhosis who underwent sclerotherapy for active GV bleeding were enrolled in the study. Among them, 218 patients received terlipressin, and 93 patients received somatostatin. The diagnostic accuracy of liver cirrhosis was confirmed by both specific admission ICD-9 codes (ICD-9-CM code 571.5 or 571.2) and inclusion in the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD. One of the following criteria is required for patients with cirrhosis to be registered in the RCIPD: (1) Intractable ascites, (2) variceal bleeding, or (3) hepatic coma or liver decompensation. Complete reports of abdominal imaging, laboratory data, and upper gastrointestinal endoscopy are required for patients to be registered in the RCIPD. The diagnostic accuracy of GV bleeding was also confirmed by specific admission ICD-9 codes (ICD-9-CM code 456.8) and inclusion in the RCIPD. Information regarding insurance-paid endoscopic sclerosis treatment was reliable because every treatment is strictly regulated by the NHIB. The choice of either somatostatin or terlipressin depends on the preferences of physicians. Comorbidities included alcoholic-related disorders (ICD-9-CM codes 291, 303, 305.00-305.03, and 571.0-571.3), diabetes mellitus (ICD-9-CM code 250), hepatocellular carcinoma (HCC) (ICD-9-CM code 155.0), acute renal failure (ICD-9-CM code 584 and 572.4), hepatic encephalopathy (ICD-9-CM code 572.2), ascites (ICD-9-CM code 789.5 or ICD-9 v3 Procedure Codes 54.91), peptic ulcer bleeding (ICD-9-CM code 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4 or 533.6), bacterial infections including pneumonia (ICD-9-CM codes 481-487, without 484), liver abscess (ICD-9-CM code 572.0), necrotizing fasciitis (ICD-9-CM code 728.86), empyema (ICD-9-CM code 510), cellulitis (ICD-9-CM code 681 or 682), central nerve system infection (including bacterial meningitis or brain abscess, ICD-9-CM code 324 or 320), sepsis (ICD-9-CM codes 038 or 790.7), infective endocarditis (ICD-9-CM code 421), biliary tract infection or acute cholecystitis (ICD-9-CM code 576.1, 575.0, 574.00, 574.01, 574.30, 574.31, 574.60, 574.61, 574.80, or 574.81), urinary tract infection (ICD-9-CM code 590.1, 595.0, 595.9 or 599.0), septic arthritis, (ICD-9-CM code 711), perianal abscess (ICD-9-CM code 566), or spontaneous bacterial peritonitis (SBP). SBP included ICD-9-CM diagnosis codes 567.2, 567.8, or 567.9, and without the procedure codes for the abdominal surgery. Death was defined as withdrawal of the patient from the NHI program.

Statistical analyses

The SPSS statistical package (SPSS System for Windows, version 13.0; SPSS Inc., Chicago, IL, USA) was used for all

statistical analyses. Student's *t*-test was used to compare continuous variables with normal distributions, and the Mann–Whitney *U*-test was used for continuous variables with non-normal distributions. The Chi-square test or Fisher's exact test was used to compare categorical variables. A proportional hazards Cox regression model was used to identify risk factors for mortality. Hazard ratios (HRs) with 95% confidence intervals (CIs) for 30-day mortality were calculated for comparisons between the terlipressin and somatostatin groups. $P < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics and treatment outcomes among subjects

In total, 311 patients with cirrhosis who underwent GVS and vasoactive drug therapy for active GV bleeding were enrolled in this study. The baseline characteristics and treatment outcomes of the patients are shown in Tables 1 and 2. In our study, 218 patients received terlipressin, and 93 patients received somatostatin. The mean patient age was 55.4 ± 12.8 years, and 75.9% (236/311) were male. The overall mortality rate at 30 days was 13.2% (41/311). The average length of hospital stay was 12.7 days. A total of 262 (84.2%) patients who underwent one session of GVS survived and were discharged. Seventy-eight (25.1%) patients received second-look endoscopy. Twelve (7%) patients received a second course of GVS, but five (5/12; 41.7%) patients died during their hospital stay.

Baseline characteristics and treatment outcomes for two different vasoactive agents

The baseline characteristics were not statistically different between the terlipressin and somatostatin groups [Table 1]. Univariate analysis was performed for clinical outcomes between the two groups and no significant differences were found regarding peptic ulcer bleeding, hepatic encephalopathy, acute renal failure, second-course histoacryl injection, second-look endoscopy, 30-day mortality, and hospital mortality [Table 2]. Patients treated with terlipressin had a higher co-infection rate (27.1% vs 14.0%, respectively, $P = 0.013$). The length of hospital stay in the terlipressin group was longer than that in the somatostatin group (14 days vs 9.6 days), but this finding was not statistically significant.

Demographics and clinical features predisposing patients to 30-day mortality

The overall 30-day mortality rates for patients treated with terlipressin and somatostatin were 13.3% ($n = 29/218$) and 12.9% ($n = 12/93$), respectively. After adjusting for age, gender, HCC, acute renal failure, hepatic encephalopathy,

Table 1: Demographic characteristics of patients treated with somatostatin compared with those treated with terlipressin

Baseline characters	Total (n=311)	Somatostatin (n=93)	Terlipressin (n=218)	P value ^a
Age				
Years	55.4±12.8	55.3±13.8	55.5±12.4	0.717
Gender, n (%)				
Female	75 (24.1)	26 (28.0)	49 (22.5)	0.313
Male	236 (75.9)	67 (72.0)	169 (77.5)	
Diabetes mellitus, n (%)				
Without	275 (88.4)	79 (84.9)	196 (89.9)	0.246
With	36 (11.6)	14 (15.1)	22 (10.1)	
Alcoholism, n (%)				
Without	200 (64.3)	59 (63.4)	141 (64.7)	0.897
With	111 (35.7)	34 (37.6)	77 (35.3)	
HCC, n (%)				
Without	225 (72.3)	72 (77.4)	153 (70.2)	0.214
With	86 (27.7)	21 (22.6)	65 (29.8)	
Ascites, n (%)				
Without	274 (88.1)	83 (89.2)	191 (87.6)	0.776
With	37 (11.9)	10 (10.8)	27 (12.4)	

^aPerformed using the Chi-square test and Mann–Whitney *U* test.

HCC: Hepatocellular carcinoma

Table 2: Clinical outcomes and concurrent disorders of patients treated with somatostatin compared with those treated with terlipressin

Characters	Total (n=311)	Somatostatin (n=93)	Terlipressin (n=218)	P value ^a
Concurrent disorder during admission, n (%)				
Co-infection	72 (23.2)	13 (14.0)	59 (27.1)	0.013
Peptic bleeding	12 (3.9)	2 (2.2)	10 (4.6)	0.521
ARF	13 (4.2)	3 (3.2)	10 (4.6)	0.761
HE	39 (12.5)	13 (14.0)	26 (11.9)	0.709
Clinical outcome, n (%)				
Hospital stay	12.7±12.0	9.6±6.7	14±13.5	0.078
Thirty day mortality	41 (13.2)	12 (12.9)	29 (13.3)	1.000
Repeat endoscopic treatment	12 (3.9)	4 (4.3)	8 (3.6)	0.756
Second-look endoscopy	78 (25.1)	22 (23.7)	56 (25.7)	0.897

^aPerformed using the Chi-square test and Mann–Whitney *U* test. ARF: Acute renal failure, HE: Hepatic encephalopathy

ascites, co-infection, peptic ulcer bleeding, alcoholism, and diabetes mellitus [Table 3], the 30-day mortality rate showed no statistically significant differences between patients treated with the different vasoactive agents ($P = 0.672$). The cumulative survival plot is presented in Figure 1. The risk

Table 3: Adjusted 30-day mortality HRs of patients with cirrhosis treated with gastric variceal sclerotherapy^a

Variable	Death/ total no.	HR	95% CI	P value
HCC				
Without	21/225	1 [Reference]	1.640-6.469	0.001
With	20/86	3.257		
ARF				
Without	35/301	1 [Reference]	2.376-16.499	<0.001
With	6/13	6.261		
HE				
Without	31/272	1 [Reference]	1.430-6.680	0.004
With	10/39	3.091		
Co-infection				
Without	30/239	1 [Reference]	0.869-3.754	0.114
With	11/72	1.806		
Vasoactive drugs^b				
Somatostatin	12/93	1 [Reference]	0.586-2.291	0.672
Terlipressin	29/218	1.159		

HCC: Hepatocellular carcinoma, ARF: Acute renal failure, CI: Confidence interval, HE: Hepatic encephalopathy, HR: Hazard ratio. ^aHRs were adjusted according to the patient's age, gender, HCC, ARF, HE, peptic ulcer bleeding, alcoholism, vasoactive drugs, ascites, and diabetes mellitus. ^bVasoactive drugs included somatostatin and terlipressin

of 30-day mortality was significantly higher in patients with HCC (HR: 3.257, 95% CI: 1.640–6.469, $P = 0.001$), acute renal failure (HR: 6.261, 95% CI: 2.376–16.499, $P < 0.001$), or hepatic encephalopathy (HR: 3.091, 95% CI: 1.430–6.680, $P = 0.004$).

DISCUSSION

Tissue adhesives including cyanoacrylate-based compounds have been used successfully for the treatment of GV. [3,17-19] The initial hemostasis control rate for GV bleeding is >90%, and the rebleeding rate is around 22%-37%. [20-23] Following GVS, the average mortality rate of GV bleeding is approximately 10%-30%. [23] This population-based study showed that the overall 30-day mortality rate was 13.2%. These data support the positive effects of endoscopic sclerotherapy to treat GV bleeding.

A single session of GV sclerotherapy (GVS) seems to be effective for the majority of patients with active GV bleeding. [17] One interesting finding of our study was the high frequency of second-look endoscopy. Although the hemostasis control rate was high (262/311, 84.2%), and only a few patients required a second procedure (12/311, 7%), one-fourth of patients had to undergo second-look endoscopy. This suggests that most endoscopists are skeptical about the treatment outcomes of sclerotherapy and recommend repeated endoscopy to confirm the therapeutic effects.

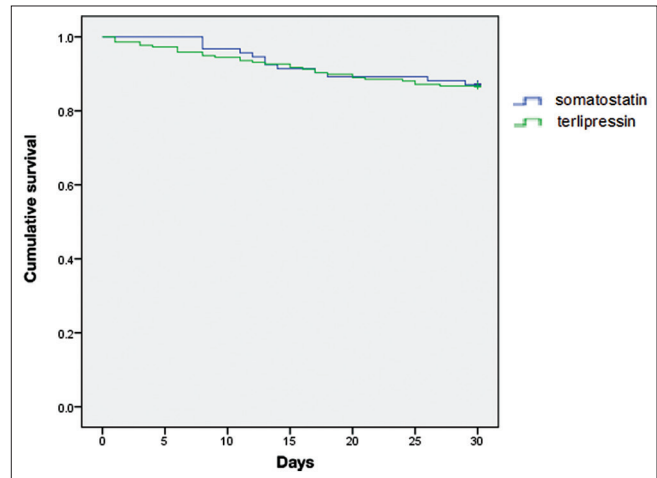


Figure 1: Cumulative survival plot for patients treated with somatostatin vs those treated with terlipressin. The 30-day survival rate showed no statistically significant differences between patients treated with terlipressin and somatostatin (86.7% vs 87.1%, respectively, $P = 1.000$)

Besides endoscopic treatment, vasoactive drugs such as octreotide, somatostatin, terlipressin, or vasopressin are recommended as soon as possible if patients are suspected of having acute variceal bleeding. [5-8] Meta-analyses have been performed, and support the efficacy of vasoactive medications in patients who experience acute variceal bleeding. [9,10] The use of vasoactive agents can lower the risk of 7-day mortality, improve hemostatic effects, decrease transfusion requirements, and shorten the duration of hospitalization. [9] One recent multicenter, randomized trial and one meta-analysis compared different vasoactive agents in variceal bleeding. [9,12] Hemostatic effects and safety did not differ significantly between study medications used as adjuncts to endoscopic treatment. However, most of these studies enrolled patients with active esophageal variceal bleeding, not GV bleeding. The choice of vasoactive drug in the treatment of acute variceal bleeding should be based on local resources. [11] The treatment choices in our country include somatostatin and terlipressin. Our population-based study investigated the treatment outcomes between two different vasoactive agents: Terlipressin and somatostatin. The overall 30-day mortality rate showed no statistically significant difference between patients treated with terlipressin or somatostatin. The present study provides evidence of similar effects of terlipressin and somatostatin for the treatment of GV bleeding after endoscopic sclerotherapy.

As in previous studies, indicators of liver dysfunction (Child–Pugh classification), HCC, and the severity of bleeding (active bleeding on endoscopy and renal function) were among the predictors of post-treatment outcomes. [12,24] Our study yielded similar results. We found elevated mortality rates in patients with HCC, acute renal failure, and

hepatic encephalopathy. These factors may be predictive for post-treatment outcomes.

Certain limitations of our study should be addressed. First, the major limitation of this study was a lack of information on clinical presentations (such as shock or active bleeding), missing basic laboratory data (such as Child–Pugh classification or MELD scoring), and endoscopic findings (such as Sarin’s classification of varices or severity of bleeding). It was not possible to calculate these scores using ICD-9 codes in the database. However, we did consider confounding factors for variceal bleeding–related mortality, such as vasoactive agents, infection, HCC, acute renal failure, hepatic encephalopathy, peptic ulcer bleeding, alcoholism, and ascites. Although unmeasured confounders may still exist in the data, we believe the methodology used in the present study is solid and robust. Second, coding errors are possible in any database, and we were unable to check diagnostic accuracy. However, the information regarding insurance-paid treatment was accurate because every treatment is strictly regulated by the NHIB.

CONCLUSION

Terlipressin and somatostatin have similar effects on mortality when they are used as adjuvants to endoscopic treatment in cirrhotic patients with acute GV bleeding. HCC, acute renal failure, and hepatic encephalopathy are associated with elevated mortality rates after endoscopic treatment. A single session of GVS is successful for controlling bleeding in the majority of patients. Although one-fourth of patients underwent second-look endoscopy, repeated GVS may be necessary in some patients.

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Conflicts of interest

There are no conflicts of interest.

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