No difference in mortality between terlipressin and somatostatin treatments in cirrhotic patients with esophageal variceal bleeding and renal functional impairment

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Objective To study the differences in mortality between terlipressin and somatostatin treatments in cirrhotic patients with esophageal variceal bleeding (EVB) and renal functional impairment (RFI).

Methods The National Health Insurance Database, part of the Taiwan National Health Insurance Program, was used to enroll cirrhotic patients who had received endoscopic variceal ligation plus somatostatin or terlipressin for EVB and who were hospitalized between 1 January 2007 and 31 December 2010. The differences in mortality between the two vasoactive agents were compared and the risk factors for 30-day mortality because of EVB were identified.

Results A total of 2324 cirrhotic patients with EVB were enrolled. The 30-day mortality data showed no significant differences between the somatostatin and the terlipressin groups ($P = 0.232$). The risk of 30-day mortality was significantly higher in male patients [hazard ratio (HR): 1.50, $P = 0.002$] and patients with hepatic encephalopathy (HR: 1.82, $P < 0.001$), ascites (HR: 1.32, $P = 0.008$), bacterial infections (HR: 2.10, $P < 0.001$), hepatocellular carcinoma (HR: 2.09, $P < 0.001$), and RFI (HR: 3.89, $P < 0.001$). A subgroup analysis of cirrhotic patients with RFI was carried out. The overall 30-day mortality was higher in patients treated with somatostatin than in those treated with terlipressin (52.6 vs. 42.3%), but the difference failed to reach significance (adjust HR: 1.49, 95% confidence interval: 0.94–2.37, $P = 0.091$).

Conclusion RFI was the most important risk factor for 30-day mortality in EVB patients. Terlipressin and somatostatin had similar effects on 30-day mortality in cirrhotic patients with EVB and RFI. Eur J Gastroenterol Hepatol 28:1275–1279

Introduction

Esophageal varices are common among patients with portal hypertension and, in particular, in cirrhotic patients [1–3]. Variceal bleeding is frequently a lethal complication of liver cirrhosis. A single episode of uncontrolled variceal bleeding results in immediate death in 5–8% of patients and has a 6-week mortality rate for at least 20% of patients [2,4]. Endoscopic variceal ligation (EVL) is recommended as the first-choice intervention for esophageal variceal bleeding (EVB) in cirrhotic patients, although sclerotherapy may be used if ligation is technically difficult [1,2,5].

If variceal hemorrhage is suspected, pharmacologic therapy with vasoactive agents should be started as soon as possible and continued for 3–5 days after endoscopic treatment [5]. Vasoactive drugs (e.g. vasopressin, somatostatin, terlipressin, and octreotide) play a role in controlling variceal bleeding by reducing portal blood flow and portal pressure. Allegedly, clinicians have no preference when selecting one of these vasoactive drugs because of their equal efficacies [6–8].

Cirrhotic patients with renal functional impairment (RFI) belong to a special subgroup of patients presenting with particularly poor clinical outcomes [9]. Vasoconstriction drugs, particularly terlipressin, combined with albumin, have been effective in the management of hepatorenal syndromes [10,11]. Terlipressin therapy may be more beneficial in improving renal function and reduce mortality than either albumin alone or no therapy [11,12]. However, the role of terlipressin in cirrhotic patients with EVB and RFI has yet to be explored.

To identify the effects of vasoactive agents on EVB-related mortality in cirrhotic patients with RFI, Taiwan's nationwide population-based dataset was used for evaluation. In addition, treatment outcomes following EVL were assessed to identify the clinical factors associated with mortality.

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Keywords: esophageal variceal bleeding, renal function impairment, somatostatin, terlipressin

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Materials and methods

This study was initiated with the 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 and all identifying personal information was removed from the secondary files before analysis.

Database

In 1995, Taiwan started the National Health Insurance (NHI) program. Currently, the NHI Bureau (NHIB) covers more than 99% of the population in Taiwan. 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, deidentified dataset 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). The privacy of patients and health care providers was protected.

Study sample

This retrospective study included patients who were discharged with a diagnosis of cirrhosis (International Classification of Diseases, 9th Revision, Clinical Modification code 571.5, or 571.2 in the database) (ICD-9-CM) between 1 January 2007 and 31 December 2007. Each patient was followed for a 3-year period starting from the time of the first hospitalization until death. In this situation, patients were only enrolled when they required EVL for EVB. In cases of multiple hospitalizations, only the first episode was included.

The primary drugs used to treat EVB in Taiwan include somatostatin and terlipressin. The two comparison cohorts included cirrhotic patients with EVB treated with either somatostatin or terlipressin. To avoid interference from measured confounding factors, a one-to-one case–control match was performed using propensity score matching (PSM) obtained from the logistic regression of somatostatin on age, sex, alcohol-related disorders, hepatocellular carcinoma (HCC), ascites, hepatic encephalopathy, RFI, and bacterial infection.

Comorbidities included alcohol-related disorders (ICD-9-CM codes 291, 303, 305.00–305.03, and 571.0–571.3), HCC (ICD-9-CM code 155.0), RFI (ICD-9-CM codes 584, 585, 586, 572.4, or other procedure codes related to renal failure), hepatic encephalopathy (ICD-9-CM code 572.2), ascites (ICD-9-CM code 789.5 or ICD-9 v3 Procedure Code 54.91), 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 codes 681 or 682), central nervous system infection (including bacterial meningitis or brain abscess, ICD-9-CM codes 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 codes 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 codes 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. Spontaneous bacterial peritonitis included ICD-9-CM diagnosis codes 567.2, 567.8, or 567.9, without the procedure codes for the abdominal surgery.

Statistical analyses

The IBM SPSS Statistics package (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, New York, USA) was used to carry out statistical analyses in this study. PSM was performed using the PSM extension program developed by Felix Thoemmes for SPSS Statistics (IBM Corp.) in 2011. The χ^2-test or Fisher's exact test was used to compare categorical variables. The Student *t*-test was used to compare continuous variables. Calculation and comparison of cumulative incidences of 30-day mortality between two vasoactive agents were performed using the Kaplan–Meier method. Differences were tested in the full time-to-event distributions between the study groups using the log-rank test. To identify risk factors for mortality, the proportional hazards Cox regression model was used to control for possible confounding factors. Hazard ratios (HRs) with 95% confidence intervals (CIs) for 30-day mortality were calculated when comparing these two groups. A *P*-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics and treatment outcomes among cirrhotic patients

Initially, a total of 3612 cirrhotic patients with EVB and who underwent EVL were identified. Of these, 1162 patients received somatostatin and 2450 received terlipressin. In the somatostatin group, all 1162 patients were enrolled. After PSM, a total of 1162 patients were included in the terlipressin group.

The baseline characteristics of the 2324 cirrhotic patients with EVB are shown in Table 1. The mean age of the enrolled patients was 55.6 ± 13.4 years; 77.5% (1801/2324) were men. The overall 30-day mortality was 17.6% (410/2324). In this study, 611 patients (26.3%) had a history of HCC, 223 (9.5%) had a history of hepatic

Table 1. Demographic characteristics of cirrhotic patients with esophageal variceal bleeding treated with somatostatin or terlipressin

	n (%)		
	Somatostatin (*N* = 1162)	Terlipressin (*N* = 1162)	*P*-value
Male	893 (76.9)	908 (78.1)	0.456
Age (years)	55.5 ± 13.7	55.7 ± 13.2	0.241
HCC	304 (26.2)	307 (26.4)	0.888
Hepatic encephalopathy	204 (17.6)	193 (16.6)	0.544
Ascites	331 (28.5)	312 (26.9)	0.378
Alcohol-related	439 (37.8)	421 (36.2)	0.439
RFI	78 (6.7)	58 (5.0)	0.077
Bacterial infection	237 (20.4)	212 (18.2)	0.189

HCC, hepatocellular carcinoma; RFI, renal functional impairment.

encephalopathy, 643 (27.7%) had a history of ascites, and 136 (5.9%) had a history of RFI. There were no significant differences between the somatostatin and the terlipressin groups in the baseline characteristics (Table 1).

Clinical features predisposing to 30-day mortality among cirrhotic patients

The overall 30-day mortality for patients treated with terlipressin versus somatostatin was 16.7% ($N=194/1162$) and 18.6% ($N=216/1162$), respectively. The 30-day mortality data showed no significant differences between the somatostatin and the terlipressin groups ($P=0.232$).

The cumulative survival plot is shown in Fig. 1. The risk of 30-day mortality (Table 2) was significantly higher in male patients (HR: 1.50, 95% CI: 1.16–1.95, $P=0.002$) and patients with hepatic encephalopathy (HR: 1.82, 95% CI: 1.45–2.29, $P<0.001$), ascites (HR: 1.32, 95% CI: 1.08–1.62, $P=0.008$), bacterial infections (HR: 2.10, 95% CI: 1.70–2.60, $P<0.001$), HCC (HR: 2.09, 95% CI: 1.69–2.60, $P<0.001$), and RFI (HR: 3.89, 95% CI: 3.00–5.03, $P<0.001$).

Baseline characteristics and clinical features predisposing to 30-day mortality among cirrhotic patients with renal functional impairment

A subgroup analysis of cirrhotic patients with RFI was also carried out. A total of 78 patients with RFI and who received somatostatin were enrolled in the somatostatin group. After PSM, 78 patients with RFI were selected from the 2450 patients treated with terlipressin and were included in the terlipressin group. No significant differences were noted in the baseline characteristics between the terlipressin and the somatostatin groups (Table 3). The overall 30-day mortality was higher in patients treated with somatostatin than in those treated with terlipressin (52.6 vs. 42.3%), but the difference was not significant (adjust HR: 1.49, 95% CI: 0.94–2.37, $P=0.091$) (Table 4). The cumulative survival plot is shown in Fig. 2.

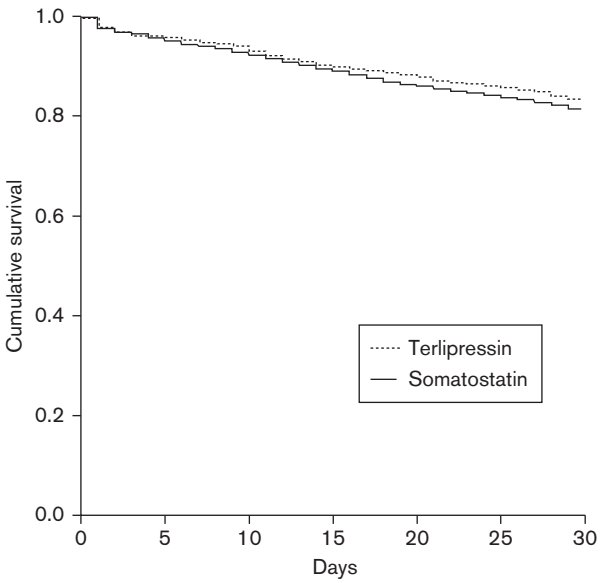

Fig. 1. Kaplan–Meier survival analysis for cirrhotic patients with esophageal variceal bleeding.

Table 2. Adjusted 30-day mortality hazard ratios for cirrhotic patients with esophageal variceal bleeding[a]

Variables	Hazard ratio	95% Confidence interval	*P*-value
Age	1.01	1.00–1.02	0.167
Male	1.50	1.16–1.95	0.002
Alcohol-related	0.91	0.71–1.17	0.461
Hepatic encephalopathy	1.82	1.45–2.29	<0.001
Ascites	1.32	1.08–1.62	0.008
Bacterial infections	2.10	1.70–2.60	<0.001
HCC	2.09	1.69–2.60	<0.001
RFI	3.89	3.00–5.03	<0.001
Somatostatin	1.09	0.89–1.32	0.409

HCC, hepatocellular carcinoma; RFI, renal functional impairment.
[a]Hazard ratios were adjusted according to the patient's age, sex, alcohol-related cirrhosis, hepatic encephalopathy, ascites, bacterial infections, HCC, RFI, and vasoactive drugs.

Table 3. Demographic characteristics of cirrhotic patients with esophageal variceal bleeding and renal functional impairment

	n (%)		
	Somatostatin ($N=78$)	Terlipressin ($N=78$)	*P*-value
Male	56 (71.8)	57 (73.1)	0.858
Age (years)	56.9 ± 12.5	57.6 ± 13.5	0.726
HCC	21 (26.9)	22 (28.2)	0.858
Hepatic encephalopathy	16 (20.5)	19 (24.4)	0.565
Ascites	31 (39.7)	32 (41.0)	0.870
Alcohol-related	23 (29.5)	19 (24.4)	0.470
Bacterial infection	21 (26.9)	21 (26.9)	1.000

HCC, hepatocellular carcinoma.

Table 4. Adjusted 30-day mortality hazard ratios for patients with esophageal variceal bleeding and renal functional impairment[a]

Variables	Hazard ratio	95% Confidence interval	*P*-value
Age	0.99	0.97–1.01	0.369
Male	2.05	1.11–3.78	0.022
Alcohol-related	0.67	0.36–1.24	0.200
Hepatic encephalopathy	1.03	0.57–1.85	0.935
Ascites	0.95	0.59–1.54	0.847
Bacterial infections	1.31	0.78–2.22	0.312
HCC	1.18	0.68–2.05	0.553
Somatostatin	1.49	0.94–2.37	0.091

HCC, hepatocellular carcinoma; RFI, renal functional impairment.
[a]Hazard ratios were adjusted according to the patient's age, sex, alcohol-related complications, hepatic encephalopathy, ascites, bacterial infections, HCC, and vasoactive drugs.

Discussion

About 30% of cirrhotic patients with esophageal varices will experience EVB during their lifetime [2,13]. Mortality rates have been reduced because of improvements in the management of patients with EVB [14], but the risk of mortality is still high. This large population-based study showed a similar poor outcome because of EVB. The overall 30-day mortality rate was 17.6%.

Besides endoscopic treatment, prophylactic antibiotics and splanchnic vasoconstrictors (such as octreotide, somatostatin, terlipressin, or vasopressin) are

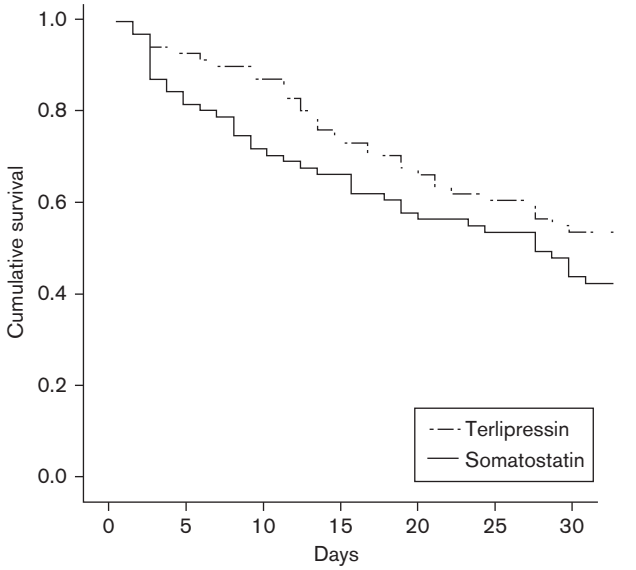

Fig. 2. Kaplan–Meier survival analysis for cirrhotic patients with renal functional impairment and esophageal variceal bleeding.

recommended as first-line treatment if patients are suspected of having acute variceal bleeding [1,2,5]. Meta-analyses support the efficacy of vasoactive medications in patients who experience acute variceal bleeding [15,16]. The use of vasoactive agents can lower the risk of 7-day mortality, improve the hemostatic effect, decrease transfusion requirements, and shorten the duration of hospitalization [15,16]. However, the choice of splanchnic vasoconstriction agents for EVB remains an important issue.

To date, cumulative randomized prospective studies had been carried out to compare the effectiveness of terlipressin and octreotide for the control of acute variceal bleeding [7,15,17–21]. All of them concluded that the efficiency of terlipressin and octreotide in controlling variceal bleeding was not different in terms of the hemostatic effect, safety, hospital stay, or mortality [15,21]. In this national population-based study, we compared the mortality between two different vasoactive agents: terlipressin and somatostatin. There were no significant differences in the 30-day mortality rate between patients treated with terlipressin versus those treated with somatostatin. We have also provided evidence on similar effects between terlipressin and somatostatin in terms of EVB after EVL. The choice of vasoactive drugs in cases of acute variceal bleeding, therefore, should be made on the basis of drug availability and the physician's experience.

As shown in previous studies, predictors of mortality include indicators of the severity of bleeding, grading of esophageal varices by endoscopy, severity of the underlying liver disease, and associated major comorbidities [22–24]. The degree to which both liver and renal functions were preserved was the most important factor affecting mortality [22,23,25]. Our findings are consistent with the results from these studies, that is, the complications from liver cirrhosis (including hepatic encephalopathy, ascites, and HCC), male sex, and associated major comorbidities (including bacterial infections and RFI) were the main risk factors associated with the 30-day mortality rate. As shown in Table 2, most of those predictive factors increased the risk of 30-day mortality, with an HR ranging from 1.3 to 2.1. However, the risk in the patients with RFI increased by about four-fold compared with that in patients without RFI (HR: 3.89, 95% CI: 3.00–5.03, $P < 0.001$). In this subgroup, nearly half of the patients (47.4%) with RFI died within 1 month.

It had been reported previously that the development of renal failure in cirrhotic patients after an EVB, which occurs in ~11% of cases, is associated with a poor prognosis [7,26]. Terlipressin therapy may improve renal function and reduce mortality in patients with hepatorenal syndrome [11,12]. However, the role of terlipressin in cirrhotic patients with EVB and RFI is still unknown. In this study, we carried out a subgroup analysis of patients with RFI. The overall 30-day mortality rate was higher in patients treated with somatostatin compared with those treated with terlipressin (52.6 vs. 42.3%), but the difference was not statistically significant. RFI is a strong indicator of liver dysfunction and the presence of RFI is sufficient to predict a poor outcome. The number of patients in this subgroup was small; therefore, future prospective studies with larger cohorts are needed to confirm our findings.

One interesting finding from our study was the sex difference in the patients with EVB enrolled in our study. The 30-day mortality rate for men was 1.5-fold greater than that for women. In general, cirrhosis is a disease that occurs predominantly in men and the postmenopausal condition in women because estrogens may have an antifibrotic effect [27]. According to an analysis by the National Center for Health Statistics in 2010, men are 1.6-fold more likely to die from chronic liver disease and cirrhosis than women after eliminating selected single causes of death [28,29]. Clinical observations and death statistics also support the view that chronic hepatitis B and C appear to progress more rapidly in men than in women [30,31]. However, the reason for the sex-associated differences in EVB has not been elucidated and further studies are needed to better understand the mechanisms underlying the sex-associated differences observed.

Our study had several limitations including its retrospective nature and the lack of clinical information (e.g. the severity of active bleeding), missing basic laboratory data (e.g. Child-Pugh classification or the Model for End-Stage Liver Disease, MELD, scores), and endoscopic findings (e.g. Sarin's classification of varices or the severity of the bleeding). We could not calculate the score of the aforementioned clinical information using the ICD-9 coding in the database. Although unmeasured confounders may exist, we believe that the case–control matching method by PSM used in the present study is solid and robust. In addition, coding errors are possible when using any database and we could not check the accuracy of the diagnosis for each patient. However, we could confirm endoscopic therapy with EVL and drug usage in the insurance-paid system, which was strictly regulated by the NHIB. The ability to perform those types of checks rendered the coding more reliable.

In conclusion, terlipressin and somatostatin exerted similar effects on mortality when used as adjuvants to endoscopic treatment in cirrhosis patients with acute EVB.

RFI was the most important risk factor for 30-day mortality in EVB patients.

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Author contributions: Tsung-Hsing Hung: material support, collected and analyzed the data, drafting of the manuscript. Chen-Chi Tsai: material support, contributed to the design of the study. Chih-Wei Tseng: contributed to the design of the study, material support, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Kuo-Chih Tseng: material support, critical revision of the manuscript for important intellectual content. Yu-Hsi Hsieh: contributed to the design of the study, critical revision of the manuscript for important intellectual content. Chih-Chun Tsai: analyzed the data.

Conflicts of interest

There are no conflicts of interest.

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