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Original Article

Risk factors for predicting in-hospital rebleeding following endoscopic variceal sclerotherapy

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Abstract: Background: This study aimed to exam the clinical risk factors of in-hospital variceal rebleeding during treatment intervals using endoscopic variceal sclerotherapy (EVS) in patients with esophageal variceal bleeding. Methods: This retrospective study included 204 cirrhosis patients with esophageal varices who received elective or emergency endoscopic sclerotherapy to prevent bleeding at the Chinese PLA General Hospital between December 2013 and June 2015. In-hospital early rebleeding was determined using endoscopy and treated using EVS. Results: The incidence of in-hospital rebleeding after EVS was 4.9%. Stepwise multivariate logistic regression analysis showed that varices erosion (OR 10.27, 95% CI 1.72-59.01, *P*=0.0128), varices size (OR 4.00, 95% CI 1.01-18.11, *P*=0.0490) and maximum sclerosing-agent volume per session (OR 1.16, 95% CI 1.04-1.32, *P*=0.0037) were independent risk factors for in-hospital rebleeding after EVS treatment. Patients with in-hospital rebleeding had a longer mean hospital stay (31.50 ± 11.85 vs. 20.50 ± 9.24 days; *P*=0.0004), higher total hospitalization costs (92217 ± 55518 vs. 34104 ± 21523 RMB; *P*<0.0001), and higher blood transfusion volume (1681 ± 1700 vs. 194 ± 141 ml; *P*<0.0001) than did non-rebleeding patients. Conclusions: In-hospital rebleeding after EVS during treatment intervals is mainly affected by varices erosion, varices size and maximum sclerosing-agent volume per session.

Keywords: Endoscopic variceal sclerosis, esophageal variceal bleeding, in-hospital rebleeding

Introduction

Esophageal variceal bleeding (EVB) is a major cause of death in patients with high portal hypertension. Currently, combined with vasoactive drugs, prophylactic antibiotics, and endoscopic techniques for treatment of EVB have markedly reduced rebleeding from 47% to 13% from 1980 to 2000 and bleeding-related death from 50% to 20% from 1960 to 2000 [1, 2]. Endoscopic therapy, including endoscopic variceal sclerotherapy (EVS) and endoscopic variceal ligation, is safe and effective for EVB with few complications [3, 4]. In China, both of these treatments are commonly used to control EVB. Nowadays, EVL is considered as the first-choice therapy to management esophageal varices for its safety and ease of use. However, the choice of endoscopic method is still mainly based on local resources and the patient's characteristics. Patients who with larger varices of initial endoscopic treatment (i.e. greater than 1.5 cm) or those who had repeated endoscopic therapy after EVS or EVL, which would not suit for EVL treatment, were performed with EVS therapy.

Previous studies have shown that patients who survive the first episode of variceal bleeding have a high risk of rebleeding and death [5]. EVS is inexpensive, easily performed, and effective therapy for controlling EVB. EVS has a high rate of control of variceal rebleeding [3, 6]. In-hospital rebleeding in patients is likely to result in a high cost for managing variceal bleeding, and may even cause a higher mortality rate than patients without rebleeding [7, 8]. Only a few studies have shown that the presence of ascites, low prothrombin activity, encephalopathy, and hyperbilirubinemia are predictive factors for early rebleeding after EVS [9, 10]. Because of the small number of cases in these previous studies, these results still need to be confirmed. Previous studies reported early re-bleeding rate still as higher as 13.6%. After EVS treatment, the patients were still at the risk of rebleeding before varices

veins completely disappear. Those parts of the rebleeding patients would have longer hospital stay and higher hospital cost and also not suitable for outpatient treatment. The timing found the risk factors of early rebleeding and successful management of patients at high risk of in-hospital rebleeding are very important. Therefore, this study aimed to examine the risk factors for in-hospital rebleeding after EVS treatment.

Methods

Enrollment of patients

A retrospective study analyzed the medical records for patients treated with EVS for esophageal varices from December 2013 and June 2015 at the Chinese PLA General Hospital. These patients with the larger diameter varices (greater than 1.5 cm) for the primary endoscopy therapy and patients undergoing either EVS or EVL therapy in the past, who were not eligible for EVL therapy, were treated with EVS for inclusion in our study. Those patients with severe jaundice, liver or renal failure, treated with EVL only and incomplete data for analyses were exclusion for further research. Medical and endoscopic records, including demographics, clinical data, laboratory data, endoscopic data, volume of blood transfusions, length of stay, and total hospital costs were reviewed throughout the hospitalization period. The diagnosis of liver cirrhosis was based on compatible clinical, laboratory, and radiological imaging findings. Portal vein thrombosis was diagnosed under the finding of a filling defect of the portal vein on abdominal ultrasonography or computed tomography.

This study was approved by the ethics committee of the Chinese PLA General Hospital. The requirement for informed consent was waived by the committee because we extracted data retrospectively from patients' medical records. No interventions or any type of study-related interaction with the patient were performed between study researchers and the individuals whose data were accessed. All data were anonymity prior to retrieval and analysis.

EVS

Evaluation of esophagogastric varices by endoscopic examination was based on a Japanese system of recording endoscopic findings of esophageal varices [11]. The location of the varices was recorded as superior, middle, or inferior based on endoscopic examination. The forms of esophageal varices were evaluated based on the shape and size of the varices, and grade of esophageal varices were evaluated according to their forms and red color sign. EVS was performed using an Olympus endoscope (HQ-260) and a 25G disposable injection needle (both from Olympus, Tokyo, Japan). Lauromacrogol (10 mg/mL; Tianyu Chang'an Corporation, Xi'an, Shaanxi Province, China) was used as the sclerosing solution and was injected into the esophageal varices from the cardia to the proximal esophagus, including the rupture point, according to the guidelines established by the Chinese Medical Association in 2009 [12]. Maximum volume for each injection was 20 mL. Among them, index endoscopy for elective EVS was performed at 7-day intervals in a sequential therapy protocol on every Wednesday or Friday in our hospital. Emergency EVS was performed within 24 hours when patients with active variceal bleeding were admitted to our hospital or rebleeding after EVS treatment occurred. Non-selective β-blockers (NSBB; carvedilol; Qilu Pharmaceutical Co., Ltd., Jinan, Shandong Province, China) were used to patients who were clinically stable after their variceal bleed. Those who had baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg or several heart failure was exclusive to receive β-blockers therapy.

Definitions

In-hospital rebleeding was considered as early rebleeding during intervals between EVS treatments and defined as the reappearance of hematemesis or melena 24 hours after an EVS treatment and before the next weekly treatment; the bleeding source also must have originated from the esophageal varices by repeat endoscopy. Child-Pugh classification grades were used to evaluate the hepatic function of patients at admission. Complete variceal eradication was defined as the obliteration of all visible varices. Partial eradication was defined as the obliteration with small vein remnants.

Data on major adverse events, including transient fever (fever >38.5°C after EVS), retrosternal pain, dysphagia, nausea and/or vomiting,

Table 1. Characteristics on admission to hospital in the in-hospital rebleeding and non-rebleeding groups

Variable	In-hospital rebleeding N=10	Non-rebleeding N=194	*P* Value
Age, years (mean ± SD)	51.90 ± 7.74	54.32 ± 11.76	0.5024
Sex, n (M/F)	7/3	145/49	0.7415
Etiology of cirrhosis, n (viral/alcohol/autoimmunity/other)	4/2/2/2	114/29/16/35	0.5883
Child-Pugh's, n (A/B-C)	3/7	117/77	0.0590
Ascites, n (none-mild/moddle-severe)	5/5	152/42	0.0561
Portal vein thrombosis, n (present/absent)	3/7	45/149	0.6301
History of surgery, n (splenectomy/splenectomy and devascularization/Spleen interventional embolization)	0/0/0	25/14/3	0.3148
History of endoscopy treatment (Y/N)	3/7	146/48	0.0035
Non-selective β-blocker treatment, *n* (Y/N)	2/8	65/129	0.3553
Digestive hemorrhage intensity, n (non/mild-moderate/severe)	0/8/2	33/117/44	0.1423
Hemoglobin, g/L (mean ± SD)	77.70 ± 17.39	94.84 ± 24.24	0.0286
White blood corpuscles, × 10^9/L (mean ± SD)	3.32 ± 1.60	3.69 ± 2.47	0.6431
Platelets, × 10^9/L (mean ± SD)	68.10 ± 28.99	109.75 ± 99.23	0.1878
Alanine aminotransferase, U/L (mean ± SD)	18.16 ± 10.48	24.49 ± 19.44	0.3085
Aspartate aminotransferase , U/L (mean ± SD)	25.78 ± 13.12	31.69 ± 21.00	0.3802
Albumin, g/L (mean ± SD)	31.94 ± 4.64	35.43 ± 6.22	0.0442
Total Bilirubin, μmol/L (mean ± SD)	25.52 ± 11.13	20.91 ± 16.97	0.3972
Direct bilirubin, μmol/L (mean ± SD)	12.22 ± 6.86	9.85 ± 13.78	0.5895
γ-glutamyltransferase, U/L (mean ± SD)	39.97 ± 23.94	62.51 ± 77.71	0.3623
Blood urea nitrogen, mmol/L (mean ± SD)	5.08 ± 1.50	4.85 ± 2.14	0.7369
Creatinine, μmol/L (mean ± SD)	63.99 ± 11.63	67.07 ± 15.94	0.5473
Thrombin time, s (mean ± SD)	17.15 ± 3.25	17.22 ± 2.45	0.9288
Activated partial thromboplastin, s (mean ± SD)	43.23 ± 4.11	42.83 ± 6.42	0.8458
Prothrombin time, s (mean ± SD)	17.36 ± 2.28	17.59 ± 6.88	0.9179

Non-small ascites, no ascites or ascites could only be detected by ultrasound examination. Middle-severe ascites, ascites causing moderate symmetrical or marked abdominal distention. EVL, endoscopic variceal ligation; EVS, endoscopic variceal sclerotherapy; F, female; M, male; Y, yes; N, no; SD, standard deviation.

abdominal pain, pneumonia, esophageal stenosis, and death were also collected based on the clinical records.

Follow up

All the patients were trying to evaluate the rate of rebleeding, re-EVS and mortality until in August 2016. Rebleeding was defined as recurrent hematemesis, and/or melena, and/or bloody fluid drained by nasogastric tube; or a decrease in hemoglobin by at least 20 g/L, or hypovolemic shock occurs. Re-EVS therapy was defined as rebleeding patients received EVS treatment or esophageal variceal patients with a higher risk factor of bleeding performed EVS therapy to prevent bleeding. Recurrence of varices was defined as the detection of varices after eradication that required prophylactic retreatment or rebleeding during follow-up. Except for re-EVS therapy, part of EVB patients received other therapies including conservative treatment, transjugular intra-hepatic portosystemic stent shut (TIPS), liver transplantation therapy.

Statistical analysis

JMP 10.0 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. Continuous variables are shown as means with SD. Continuous parameters between the two groups were analyzed using analysis of variance and the Student's *t* test. Proportional data were compared using the Fischer's exact test and x^2 test. Forward stepwise logistic regression analysis was performed to identify independent risk factors for in-hospital rebleeding after EVS. *P* values <0.05 were considered significant. All data were managed anonymously.

Results

Patients' characteristics

A total of 204 cases under EVB treatment were included in this study. Among the patients

Table 2. Endoscopic findings in the in-hospital rebleeding and non-rebleeding groups

Variable	In-hospital rebleeding (N=10)	Non-rebleeding (N=194)	*P* value
Varices grading, n (GI/GII/GIII)	0/0/10	3/23/168	0.2465
Varices form, n (F1/F2/F3)	0/3/7	19/42/133	0.5150
Red spots, n	10	183	0.2862
Erosion, *n*	3	12	0.0265
Extent of varices, n (supper/middle-lower)	7/3	57/137	0.0100
Size of varices, cm (mean ± SD)	1.62 ± 0.54	1.12 ± 0.52	0.0036
Number of varices (≤3/>3)	2/8	111/83	0.0187
Gastric varices, n	4	67	0.7261
Maximum volume of sclerosing per session, ml (mean ± SD)	40.40 ± 5.15	32.25 ± 9.18	0.0059

Form of the esophageal varices: F1, small and straight; F2, nodular; F3, large and coided. Grade of the esophageal varices: G1, F1 without red color sign; G2, F1 with red color sign, or F2 without red color sign; G3, F2 with red color sign, or F3 with or without red color sign. Extent of varices: S/M-I, extent of varices located in the superior/middle to inferior region, respectively; SD, standard deviation.

Table 3. Univariate and multivariate analyses of risk factors for EVB patients with in-hospital rebleeding

Variable	Univariate analysis			Multivariate analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Hemoglobin	0.1422	0.97	0.92-1.01			
Albumin	0.6484	0.97	0.83-1.11			
Erosion	0.0410	7.31	1.09-47.15		10.27	1.72-59.01
Number of varices	0.5730	1.70	0.28-14.43			
Extent of varices	0.3591	2.08	0.44-11.74			
Size of varices	0.2333	3.38	0.44-24.38	0.0490	4.00	1.01-18.11
Maximum volume of sclerosing per session	0.0696	1.13	0.99-1.30	0.0037	1.16	1.04-1.32
History of endoscopy treatment	0.9425	0.94	0.13-5.53			

OR = odds ratio; CI = confidence interval.

included, 10 patients with in-hospital recurrent hemorrhage were classified as the in-hospital rebleeding group (4.9%) and the other 194 patients without recurrent hemorrhage were classified as the non-rebleeding group (95.1%).

Characteristics of EVB patients with in-hospital rebleeding and those without rebleeding

There were no significant differences in age, sex, etiology of portal hypertension, Child-Pugh classification, ascites, portal vein thrombosis, NSBB used, intensity of digestive hemorrhage before admission, and history of surgery between the two groups (**Table 1**). Additionally, there were no differences in the amount of white blood corpuscles and platelets, levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, γ-glutamyltransferase, urea, and creatinine, and thrombin time and prothrombin time between the two groups (**Table 1**). Patients who had a history of endoscopic therapy in EVS treatment were more likely to have in-hospital rebleeding (*P*=0.0035). The in-hospital rebleeding group had lower hemoglobin (*P*=0.0286) and albumin levels (*P*=0.0442) than the non-rebleeding group.

Endoscopic findings difference between in-hospital rebleeding and those without rebleeding

In univariate analysis, varices erosion, extent of varices in veins, the size of varices, number of varices, and maximum volume of sclerosing agent per session had a significant effect on the in-hospital rebleeding rate (**Table 2**).

Multivariate analyses of risk factors of in-hospital rebleeding

The significant candidate variables (hemoglobin, albumin, varices erosion, number of varices, extent of varices, size of varices, maximum

Table 4. Outcomes of the in-hospital rebleeding and non-rebleeding groups

Variable	In-hospital rebleeding N=10	Non-rebleeding N=194	*P* value
Treatment frequency (<4/≥4), n	6/4	155/39	0.1628
EV completely disappear/partly disappear/non-disappear, n	4/5/1	51/141/2	0.1530
Complications, *n* (%)			0.1756
None to mild	8 (80.00)	175 (90.21)	
Moderate to severe	1 (10.00)	18 (9.28)	
Death	1 (10.00)	1 (0.52)	
Ulcer, n (%)	9 (90.00)	165 (85.05)	0.8110
Length of stay, days (mean ± SD)	31.50 ± 11.85	20.50 ± 9.24	0.0004
Total charges, RMB (mean ± SD)	92217 ± 55518	34104 ± 21523	<0.0001
Total transfusion of blood, ml (mean ± SD)	1681 ± 1700	194 ± 141	<0.0001

EV, esophageal varices; SD, standard deviation.

Table 5. Follow up of patients in-hospital bleeding

Variable	In-hospital rebleeding (N=6)	Non-rebleeding (N=168)	*P* value
Rebleeding, n (Y/N)	1/5	10/158	0.3687
Re-EVS therapy, n (Y/N)	3/3	53/108	0.3974
Death, n (Y/N)	0/6	3/165	0.6449
Other therapy*, n (Y/N)	0/6	7/161	0.4788

*Other therapy including conservative treatment, transjugular intra-hepatic portosystemic stent shut (TIPSS), liver transplantation therapy; Y, yes; N, no.

volume of sclerosing agent per session and history of endoscopic therapy) that were identified by univariate analysis were then submitted to binary logistic regression (forward stepwise) analysis. Multivariate analysis showed that having erosion of esophageal varices (OR 10.27, 95% CI 1.72-59.01, *P*=0.0128), lager size of varices (OR 4.00, 95% CI 1.01-18.11, *P*=0.0490) and a higher maximum volume of sclerosing agent per session (OR 1.16, 95% CI 1.04-1.32, *P*=0.0037) were independent predictive factors for in-hospital rebleeding after EVS treatment (**Table 3**).

Outcomes of patients with in-hospital rebleeding and those without rebleeding

There were no significant differences in the frequency of repeat treatment and the rate of eradication of esophageal varices between the two groups (**Table 4**). In addition, complications between the two groups were not significantly different (*P*=0.1756). Furthermore, the occurrence of esophageal ulcers was the same in the two groups. The in-hospital rebleeding group had significantly higher hospital costs (*P*<0.0001), a longer hospital stay (*P*=0.0004), and a higher blood transfusion volume (*P*< 0.0001) compared with the non-rebleeding group (**Table 4**).

Follow up of patients in-hospital rebleeding

During follow up, a total of 30 out of 204 patients were lost to follow up. Among them, three patients were dead: one patient was dying of severe pneumonia, one patient was dying of gallbladder carcinoma, and one patient was dying of hepatic encephalopathy. Follow-up data for 9.8 ± 6.9 months (range 0.5-40.3 months) of EVS patients (**Table 5**). There was no difference between the groups in the rate of rebleeding, re-EVS and mortality. The other therapies in non-rebleeding group were not significantly different compared to in-hospital rebleeding group.

Discussion

Variceal rebleeding occurs in 60% of patients in the first 2 years and causes mortality in up to 33% patients who survive an episode of variceal hemorrhage. With advances in technology, endoscopic therapy has become an integral tool for managing acute variceal bleeding, as well as preventing recurrent bleeding [3, 6]. However, after endoscopy treatment, rates of rebleeding from esophageal varices are still as high as 13.6% [2, 13]. Currently, there is no general consensus on the risk factors of in-hospital rebleeding for patients who are treated by

EVS. In our study, we found that the in-hospital rebleeding rate during sclerotherapy treatment sessions was mainly affected by erosion of esophageal, varices size of varices and the maximum volume of sclerosing agent per session.

In-hospital recurrent bleeding affects patients with EVB during the intervals between EVS treatment sessions. The incidence of in-hospital rebleeding after EVS greatly varies among different studies. In Sung et al's study, initial control of bleeding with emergency EVS was 90%, with a rebleeding rate of 16% within 48 hours [14]. Villanueva et al found that the in-hospital rebleeding rate was 9% 24 hours after admission and within the first 5 days [15]. However, another study showed that the rebleeding rate was as high as 40% after EVS treatment during a 6-week follow-up period [16]. The in-hospital rebleeding rate was higher in these previous studies than in our study. The difference in the in-hospital rebleeding rate in our study and previous reports could be due to the difference in the time spans used to measure post-treatment rebleeding. In the present study, we focused on assessing the predictors of in-hospital recurrent bleeding in patients with EVB between 24 hours after sclerotherapy treatment and before the next routine treatment. However, most of the previous studies defined in-hospital rebleeding between 48 hours to 6 weeks after EVS treatment. Another reason for the difference in rebleeding rate between studies might be based on whether patients with EVB had elective or emergency treatment.

To date, few studies have reported risk factors of in-hospital rebleeding after treatment with EVS. Previous studies have reported several predictive indicators of in-hospital rebleeding after EVS treatment, including active bleeding at endoscopy [13], high blood urea nitrogen levels, low albumin levels, infection [17], and poor Child-Pugh grade [18]. However, there were no significant differences in most variables between the in-hospital rebleeding and non-rebleeding groups in our study. In addition, other characteristics, such as severity of esophageal variceal grading and portal vein thrombosis, did not show any significant association with recurrent hemorrhage after EVS during treatment intervals. In the present study, we found that varices erosion, varices size and maximum sclerosing-agent volume per session were associated with in-hospital rebleeding after EVS treatment sessions.

Avgerinos et al showed that EVS treatment had a higher rebleeding rate because of a sustained increase in hepatic venous pressure gradient [16]. A large size of varix indicates a higher wall tension and has the highest risk of rupture with the appearance of red spots (indicates reduced wall thickness), which is directly related to portal pressure [19]. A previous study demonstrated that the group of patients with a larger volume of sclerosing injection use had a higher rate of rebleeding compared with the small volume group (15.8% vs. 0%) [20]. Our study also showed that a larger size of esophageal varices in patients with EVB tended to fill with more sclerosing solution. This situation, in addition to hypertension of the esophageal vein after EVS, induced a high rebleeding rate. Reviews have emphasized that a high portal pressure, a large variceal radius, and the presence at endoscopy of large varices with red spots are correlated with the risk of esophageal variceal bleeding [21, 22]. Therefore, reducing portal hypertension by drug therapy (e.g., somatostatin) before and after EVS treatment might prevent in-hospital rebleeding.

Currently, concept of the explosion theory, where varices bleeding probably occurs when the expanding force by pressure and flow can no longer be counter-balanced by the variceal wall tension, was globally considered as pathophysiological mechanisms for the varices rupture and bleed [23]. However, the lesion of esophageal varices which was presented as erosion overlying the varices, still considered as the sign of bleeding arises from gastroesophageal variceal [24, 25]. In our study, we also indicated that varices erosion was the risk factor for in-hospital rebleeding. Indeed, variceal erosion on the varices is risk factor predicting increased variceal rupture rate from an external trauma eroding the thin and fragile wall of the varices [26]. As previous studies showed that esophagitis, subsequent ulceration and even deglutition of solid food were suggested erosives [26]. Therefore, those patients with erosion varices can be utilized prolonged proton pump inhibitor use, and strengthened dietary guidance and health education before and after EVS therapy.

EVS is an invasive endoscopic procedure. There were several complications associated with this technique in our study. The difference in complications between the in-hospital rebleeding and non-rebleeding groups might have caused the higher mortality rate in the in-hospital rebleeding group. In addition, the rate of development of esophageal ulcers is similar to previous studies [27], and was not significantly different between the in-hospital rebleeding and non-rebleeding groups.

To estimate the costs of in-hospital rebleeding and non-rebleeding after EVS treatment, the number of hospital days, hospital costs, and volume of blood transfusions were further analyzed. The in-hospital rebleeding group had an average of 1.5 more days in hospital, a 2.7-fold higher in-hospital cost, and an 8.7-fold higher transfusion volume compared with the non-rebleeding group. If we can predict the risk factors of in-hospital rebleeding, we can greatly reduce the costs and length of stay per hospitalization, and also reduce the use of blood products.

A limitation of our study was that there was relatively few cases of in-hospital rebleeding, which reduced the power of our statistical analysis to compare the two groups. In the future, more samples will need to be collected to address this issue.

In conclusion, our study shows that the risk factors for in-hospital rebleeding during intervals of EVS were varices erosion, varices size and maximum sclerosing-agent volume per session. Additionally, in-hospital rebleeding is associated with a longer hospital stay, higher hospital costs and greater blood transfusion volume. Ultimately, before EVS is performed, we should carefully control portal vein pressure, and then may enhance endoscopic management of esophageal varices by reducing complications and conserving medical resources.

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Disclosure of conflict of interest

None.

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