Original Article

Compliance with Guidelines of Using Vasoconstrictors in Patients with Acute Esophageal Variceal Bleeding

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Objective: Vasoconstrictors are generally required to achieve hemostasis for patients with acute variceal bleeding. This study aimed at comparing the compliance of our hospital staff with the guidelines on vasoconstrictor use in two patient cohorts with acute variceal bleeding and assessing whether use of vasoconstrictors may enhance hemostasis.

Methods: Cirrhotic patients presenting with variceal bleeding at E-Da Hospital between 2005 − 2006 and 2012 were prospectively enrolled to evaluate the compliance of combinating band ligation with vasoconstrictor use and its impact on rebleeding.

Results: 2005 − 2006 cohort comprised 90 patients and 2012 cohort comprised 113 patients. In the 2005 − 2006 cohort, only 81 of 90 (90%) patients received vasoconstrictors, whereas 107 of 113 (95%) patients in the 2012 cohort received vasoconstrictors (p = 0.90). Pre-endoscopic vasoconstrictors were prescribed in 37 of 90 (41.1%) patients in the 2005 − 2006 cohort, and in 67 of 113 (59.2%) patients in the 2012 cohort (p = 0.001). Of all 188 patients receiving vasoconstrictors, 14 (7.5%) experienced variceal rebleeding, whereas no variceal bleeding was noted in the 15 patients without receiving vasoconstrictors (p = 0.61). The survival rate of patients with and without receiving vasoconstrictors was 89% and 95%, respectively (p = 0.85).

Conclusions: The compliance with guidelines on vasoconstrictor use in patients with acute variceal bleeding was considerably high in both cohorts. However, the combination of vasoconstrictors with banding ligation did not appear to enhance hemostasis and survival.

Key words: banding ligation, vasoconstrictors, variceal bleeding

Introduction

Hemorrhage from gastro-esophageal varices is a devastating complication of portal

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hypertension. The in-hospital mortality of acute variceal bleeding was up to 40% about two decades ago, and was reduced to about 15 − 20% in recent years.[1-3] Vasoconstrictors have been shown to control approximately 80% of bleeding episodes and are generally used as a first line therapy.[4-5] Previous studies showed that combination of endoscopic therapy with vasoconstrictor is superior to either vasoconstrictor or endoscopic therapy alone in achieving successful hemostatsis of bleeding varices.[6-7] However, not only does combination therapy fail to improve 5-day or 42-day mortality, but it may also be associated with increased adverse events.[7]

Prior to endoscopic therapy, the use of vasoconstrictors has been proved to reduce the incidence of active bleeding during emergency endoscopy, facilitating the performance of endoscopic therapy and hemostasis.[8-9] Endoscopic therapy is usually indicated when the diagnosis of acute bleeding varices is confirmed.[10] Following endoscopic therapy, vasoconstrictors are generally recommended to continue for 3 − 5 days to prevent very early rebleeding.[4,11] Owing to the superiority in efficacy and safety, terlipressin and somatostatin are considered the first choice.[4]

Since endoscopic variceal ligation (EVL) is highly effective in acute hemostasis, it has replaced sclerotherapy as the endoscopic therapy of choice for acute esophageal variceal hemorrhage.[12-13] The role of vasoconstrictors after successful hemostasis achieved by EVL has rarely been investigated. Thus, this retrospective study aimed at assessing the compliance of clinicians with the guidelines on vasoconstrictor use and to evaluate whether the use of vasoconstrictors after endoscopic therapy could enhance hemostasis in an acute setting.

Subjects and Methods

The study included two cohorts. The first cohort included patients admitted between January 2005 and December 2006. The second cohort included patients admitted between January and December 2012. The selection of these two cohorts was based on the assumption that the compliance of using vasoconstrictors might be markedly different after most guidelines adopting the principles of combining vasoconstrictors and EVL since 2005. Inclusion criteria were cirrhotic patients presenting with either hematemesis or melena (or both) at our hospital with the diagnosis of acute variceal hemorrhage through emergency endoscopy and receiving endoscopic therapy with either glue injection or banding ligation. Acute gastro-esophageal variceal bleeding was defined as: 1) active spurting or oozing of blood from a varix or 2) stigmata of recent hemorrhage such as blood clots coating on the varices or the presence of hematocystic spots, erosive spots or white nipples on a varix. Exclusion criteria were: 1) association with fever > 37.5°C, bacterial infections or sepsis on admission for index bleeding; 2) patients not hospitalized for index bleeding; 3) patients presenting with variceal bleeding on admission for other co-morbidities; 4) inadequate clinical data. The diagnosis of cirrhosis was based on clinical history, biochemical and laboratory data, ultrasound or radiological findings, or histological examination.

After endoscopic therapy, the patients were generally hospitalized for further supportive management. Clinical evaluation including complete blood count, Child-Pugh's classification, renal function, serum alpha-fetoprotein and ultrasound of upper abdomen was routinely performed. Standard therapy, including blood and frozen plasma transfusion, fluid and electrolytes replacement, was given if clinically indicated. The use of vasoconstrictors was at the discretion of the physician. All endoscopists have been well trained and had experience in both glue injection of gastric varices and ligation of esophageal vari-

ces. The size of esophageal varices was determined based on Beppu's classification. Endoscopic findings, therapeutic strategies and chart records of eligible subjects were reviewed for baseline data, amount of blood transfusion, use of vasoconstrictors and prophylactic antibiotics as well as treatment outcomes and complications. The Child-Pugh's scores were calculated from the data of initial presentation. Our study was approved by the IRB of our hospital.

Our methods of endoscopic variceal ligation for esophageal varices and glue injection for gastric varices were similar to those described previously.[12] Briefly, premedication with 20 mg of buscopan was given intramuscularly. A pneumatic-active ligating device (Sumitomo, Tokyo, Japan) was attached to the endoscope (XQ 230, Olympus, Tokyo, Japan) and an overtube was used. Ligation was performed at the active bleeding site, hematocystic spots, or erosive spots over the varices.

Commercial needles (NM-1k, Olympus, Tokyo, Japan) were rinsed with distilled water and lipiodol before and after injection. The obturation agent was n-butyl-2-cyanoacrylate (Histoacryl; B.Braun, Melsungen AG, Germany) 0.5 mL mixed with 0.5 mL Lipiodol ultra-fluide (Guerbet, Bois Cedex, France). If active bleeding was encountered during endoscopic procedure, the injections were focused on the bleeding sites. For patients with gastric varices without active bleeding, the injections were targeted at the hematocystic spots or the erosive spots on the culprit varix.

Definitions of initial hemostasis, very early rebleeding and treatment failure

Initial hemostasis was defined as achieving a 24-hour bleeding-free period within the first 48 hours after treatment together with stable vital signs based on modified Baveno consensus criteria.[14] Very early rebleeding was defined as upper gastrointestinal bleeding that occurred after initial hemostasis and within five days after enrollment. Treatment failure was defined as failure to control acute bleeding episodes or very early rebleeding. Diagnosis of cirrhosis was made based on history, physical examinations, imaging studies or histological examination.

Statistical analysis

The data were expressed as mean ± S.D. Statistical analysis was based on an intention-to-treat principle. Quantitative variables were compared using Student's t-test, and qualitative variables were compared with Chi-square test and Fisher's exact test where appropriate. All P values were two-tailed. P value < 0.05 was considered significant. Analyses were performed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

Results

In the 2005 − 2006 cohort, a total of 252 patients were screened and 90 patients were included. In the 2012 cohort, 210 patients were screened and 113 patients were included. The baseline clinical data of both cohorts are shown in Table 1. Both groups were comparable in baseline characteristics including the etiologies of cirrhosis, severity of liver disease expressed as Child-Pugh's scores, incidence of esophageal variceal bleeding and gastric variceal bleeding as well as the use of vasoconstrictors. However, the 2005 − 2006 cohort had a higher percentage of male patients and hemoglobin level, whereas a higher systolic blood pressure and larger amount of blood transfusion prior to endoscopic therapy were noted in the 2012 cohort.

In the 2005 − 2006 cohort, only 81 out of 90 (90%) patients received vasoconstrictors, whereas 107 of 113 (95%) patients in the 2012 cohort received vasoconstrictors. The difference was statistically insignificant ($p = 0.28$). Terlipressin and somatostatin were used in 100% and 0% of patients receiving vasoconstrictors in the 2005 − 2006 cohort, respec-

Table 1. Baseline data of subjects enrolled in the two cohorts

	2005 − 2006 cohort (n = 90)	2012 cohort (n = 113)	*p* value
Age	52.07 ± 11.90	53.7 ± 12.61	0.35
Sex			0.03
Male	83 (92.2%)	93 (82.3%)	
Female	7 (7.8%)	20 (17.7%)	
Systolic pressure (mmHg)	117.48 ± 20.41	125.42 ± 29.13	0.02
GPT (U/L)	69.22 ± 86.40	56.42 ± 104.42	0.35
Hemoglobin (g/dL)	9.28 ± 2.46	8.40 ± 2.22	0.01
WBC (10^3/μL)	8.70 ± 4.01	7.63 ± 3.42	0.05
Platelets (10^3/μL)	116.50 ± 72.82	114.27 ± 62.83	0.82
Creatinine (mg/dL)	1.24 ± 0.55	1.38 ± 1.00	0.22
Etiology of Cause			0.42
Alcohol	36 (40%)	35 (31%)	
HBV	27 (30%)	31 (27.4%)	
HCV	22 (24.4%)	39 (34.5%)	
HBV + HCV	3 (3.3%)	3 (2.7%)	
Others	2 (2.2%)	5 (4.4%)	
Child-Pugh score			0.77
A	19 (21.1%)	28 (24.8%)	
B	42 (46.7%)	48 (42.5%)	
C	29 (32.2%)	37 (32.7%)	
EV bleeding	53 (58.9%)	83 (73.5%)	0.03
GV bleeding	37 (41.1%)	30 (26.5%)	0.03
Vasoconstrictors	81 (90%)	107 (94.7%)	0.21
Blood transfusion before endoscopy (units)	0.97 ± 1.21	2.11 ± 2.69	< 0.05
Blood transfusion after endoscopy (units)	2.78 ± 5.36	4.45 ± 6.97	0.06
Hospitalization (days)	8.46 ± 5.93	9.75 ± 8.84	0.23

GPT: Glutamic pyruvic transaminase; WBC: White blood cell; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EV: Esophageal varices; GV: Gastric varices

tively, and 98% and 2% of patients in the 2012 cohort vasoconstrictors, respectively. Pre-endoscopic vasoconstrictors were prescribed in 37 of 90 (41.1%) patients in the 2005 − 2006 cohort, and in 67 of 113 (59.2%) patients in the 2012 cohort (p = 0.001). The vasoconstrictors were administered for 3 days in both cohorts.

In the 2005 − 2006 cohort, 31 out of 37 (83.7%) patients who received pre-endoscopic vasoconstrictors had active bleeding on undergoing endoscopy, whereas 39 out of 44 (88.6%) patients who did not receive pre-endoscopic vasoconstrictors had active bleeding when receiving endoscopy (p = 0.73). In the 2012 cohort, 52 out of 67 (77.6%) patients who received pre-endoscopic vasoconstrictors had active bleeding when undergoing endoscopy, whereas 33 out of 40 (80.2%) patients who did not receive pre-endoscopic vasoconstrictors had active bleeding during endoscopy (p = 0.82). If pooled together, among the patients receiving vasoconstrictors, 14 of 188 (7.5%) experienced variceal rebleeding, whereas 0 of 15 (0%) patients without vasoconstrictor experienced variceal rebleeding (p = 0.61). Child-Pugh scores were similar between patients with vasoconstrictors and those without. The survival rate at discharge was 89% for patients with vasoconstrictor treatment and 93% for those without (p = 0.85). No significant difference in survival rate existed between patients using vasoconstrictors and patients without vasoconstrictors.

Discussion

Hemorrhage from gastro-esophageal varices is a devastating complication of portal hypertension. The treatment of acute variceal hemorrhage has advanced greatly in recent two decades. One of the most important advancement could be attributed to the combination of endoscopic therapy and vasoconstrictors to achieve a higher rate of hemostasis in an acute setting.[7,13] A meta-analysis comparing endoscopic therapy plus vasoconstrictor and endoscopic therapy alone revealed an initial hemostasis rate of 88% and 76% for

the former and latter, respectively. The corresponding 5-day hemostasis rate was 77% vs. 58%, respectively.[7] The results suggested that association of vasoconstrictors with endoscopic therapy significantly enhanced 5-day hemostasis. However, mortality was not significantly reduced by the combination therapy. Several international guidelines including Baveno consensus, AASLD guidelines as well Taiwan Gastroenterology Society guidelines all recommended the combination of vasoconstrictors, endoscopic therapy and prophylactic antibiotics for the treatment of acute variceal bleeding.[4,14] Since the compliance of clinicians with these treatment guidelines has rarely been investigated. Our previous study on the use of prophylactic antibiotics in patients with acute variceal bleeding showed that use of prophylactic antibiotics was indeed significantly increased in recent years.[15] On the other hand, contrary to the results of previous reports,[4] the use of prophylactic antibiotics had no significant impact on the incidence of rebleeding and patient survival in the present study.[15]

The purposes of this study are to examine the compliance of clinicians with the guideline on vasoconstrictor use and its impact on the outcomes of patients presenting with acute variceal bleeding. Our study included two cohorts. While one cohort included patients hospitalized between 2005 and 2006, the other cohort enrolled patients hospitalized in 2012. The proportion of female patients increased significantly in 2012. The mean hemoglobin level was lower in the 2012 cohort and the amount of blood transfused before endoscopy was thus significantly higher in the 2012 cohort compared to those in the 2005 − 2006 cohort.

It is a general belief that endoscopic therapy is the mainstay of treatment for acute esophageal variceal hemorrhage.[12] EVL is currently the endoscopic therapy of choice for bleeding esophageal varices. Hemostatic rates achieved by EVL in patients with active esophageal variceal hemorrhage were usually higher than 90%. The role of vasoconstrictors after successful hemostasis achieved by EVL is still unknown. The compliance of clinicians with the guidelines on vasoconstrictor use and its impact on rebleeding in the real world scenario has rarely been investigated.

Our study showed that the compliance was 90% in the 2005 − 2006 cohort and 95% in the 2012 cohort. The increase was not statistically significant, suggesting that vasoconstrictors have been widely prescribed in patients with acute variceal bleeding since a decade ago. However, pre-endoscopic use of vasoconstrictors was only 41.1% in the 2005 − 2006 cohort, and 52.2% in the 2012 cohort. These data suggested that the use of vasoconstrictors was usually initiated after instead of before endoscopic therapy at our hospital. The proportion of using pre-endoscopic vasoconstrictors has been increasing in recent years. However, this figure showed very low compliance as compared with a study carried out in the United States.[16] The present study showed that the incidence of active bleeding at endoscopy was not affected by the use of pre-endoscopic vasoconstrictors. Moreover, this factor did not have significant impact on the control of variceal bleeding. Contrary to general belief, it is interesting to find that the use of vasoconstrictors was associated with neither a reduced rebleeding nor an improved survival. The rebleeding rate was 7.5% in patients receiving vasoconstrictors and 0% in patients without vasoconstrictors. The lower rebleeding rate in patients without vasoconstrictors may be simply due to the skill of endoscopic hemostasis of the physicians in charge. The other possibility was that patients without vasoconstrictors may experience less severe bleeding which was easily controlled by endoscopic therapy alone. Our data were different from those in previous reports. Several factors may explain the discrepancy. Firstly, this may be due to inadequate sample size. Pooled together, only 15 patients did not receive vasoconstric-

tor. Secondly, since this is a retrospective analysis, some cases may be excluded inadvertently. Thirdly, the dose of vasoconstrictors was usually lower than that in other reports.[17-18] Terlipressin 1 mg every 6 hours was most frequently adopted at our hospital instead of 2 mg every 4 hours administered in western countries. Finally and possibly most importantly, all of our patients received EVL instead of sclerotherapy to treat esophageal varices. Our previous study suggested that emergency EVL is superior to sclerotherapy in terms of hemostasis and complications.[2,12] Our hemostatic rates were up to 92.5% − 100%, significantly higher than 58% − 77% reported in a meta-analysis.[7] Our prospective study using proton pump inhibitors instead of vasoconstrictors in patients achieving acute hemostasis by banding ligation suggested that both methods were similarly effective, with hemostasis rate ranging between 96% and 98%.[19] It is good to find that most clinicians at our hospital were compliant with practice guidelines to combine EVL with vasoconstrictors for patients with variceal bleeding. High compliance with guideline generally represents good health care quality management. However, it is surprising to find that a high degree of variation on the use of systemic vasoconstrictors and prophylactic antibiotics in the process of care has not been associated with increased mortality from acute variceal hemorrhage.[15,20]

In conclusion, the compliance with guidelines on vasoconstrictor use in patients with acute variceal bleeding was appreciably high in both cohorts. However, the proportion of pre-endoscopic vasoconstrictor use remains quite low even in recent years. Contrary to general belief, the combination of vasoconstrictor with banding ligation did not appear to enhance hemostasis and survival. Our real-world data did not prove the additive effect offered by vasoconstrictor use in patients receiving effective endoscopic therapies. A prospective study with larger sample size is still required to verify the synergistic effect of combining vasoconstrictor use with banding ligation on hemostasis in patients with acute variceal bleeding.

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