A Study into the Characteristics and Outcome of Variceal Bleeding in a Tertiary Hospital in Southeast Asia

B S Yew, MRCP*, W C Ong, MRCP, W C Chow, MRCP, H F Lui, FRCP

Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Road, Singapore 169608

SUMMARY

This retrospective study evaluated patients admitted to the Department of Gastroenterology, Singapore General Hospital for variceal bleeding in the year 2004. Improvement in outcome of variceal bleeding has been reported in the West. There is no regional data on this condition. This study aims to determine the characteristics and outcome of variceal bleeding in a tertiary hospital in Southeast Asia. Twenty-two patients were eligible. The main aetiologies of liver cirrhosis were chronic hepatitis B (38%) and alcohol (33%). Child's A, B and C were 29%, 48% and 24% respectively. Nineteen patients (86%) had bleeding oesophageal varices (band ligation performed). The remaining three patients (14%) had bleeding gastric varices (N-butyl-2-cyanoacrylate injection performed). Detailed description of certain endoscopic findings was absent in up to 18 patients (82%). All patients received antibiotics and vasoactive drug. In-hospital mortality and rebleeding were 9% and 18% respectively. We conclude that the relatively low in-hospital mortality and rebleeding rates in our series are most probably due to the smaller proportion of patients with severe liver dysfunction and management which adhered to recommendations. Documentation of endoscopic findings needs to be improved to facilitate the continuation of care.

KEY WORDS:
Variceal bleeding, Cirrhosis, Oesophageal varices, Mortality, Rebleeding

INTRODUCTION

Liver cirrhosis is the most common cause of portal hypertension which in turn, is responsible for complications such as oesophago-gastric varices, ascites, hepatorenal syndrome and hepatic encephalopathy. Bleeding from oesophago-gastric varices is the major source of morbidity and mortality in patients with cirrhosis. It is a relatively common condition and accounts for up to 10% of all upper gastrointestinal bleeding[1]. The most important predictive factors related to the risk of variceal bleeding are variceal size, the presence of red wale sign and the severity of liver dysfunction[2]. The prevalence of oesophageal varices in cirrhotic patients is high. They are present in 40% of patients with compensated liver cirrhosis and 60% of those with ascites[3]. Once diagnosed, the overall incidence of variceal bleeding is in the order of 25% at two years in non-selected cirrhotic patients[4]. The mortality rate from the first variceal bleed is high. Approximately 30%-50% of cirrhotic patients die within six weeks of a first variceal bleed[5]. Over the past decades a number of new pharmacological, endoscopic, radiological and surgical therapies have been introduced and these have led to an improvement in the management of variceal bleeding. Several recent studies[5-9] from Europe and North America have reported a decrease in the mortality rate of variceal bleeding in the past few decades. For example, El-Serag and Everhart[6] reported that the mortality at 30 days from a first variceal bleed declined from 29.6% to 20.8% between 1981-82 and 1988-91.

There is risk of rebleeding after the first variceal bleed and the reported incidence of early rebleeding ranges between 30% and 40% within the first six weeks. The risk is greatest in the first five days, then declines slowly over the first six weeks, and becomes virtually equal to that before bleeding occurred after the sixth week[4]. Furthermore, the rebleeding rate at one year is more than 60%[10].

Although variceal bleeding is an important and relatively common condition, there is however no regional data on the outcome of this condition. This data is important especially in the light of recent improvement in the management of variceal bleeding. We therefore conducted this study to determine the characteristics and outcome of variceal bleeding in a tertiary hospital in Southeast Asia.

MATERIALS AND METHODS

Study cohort

This retrospective study included all consecutive patients admitted to the Department of Gastroenterology in Singapore General hospital (SGH) for variceal bleeding in the year 2004. Patients with non-variceal upper gastrointestinal bleeding were excluded from the study. The patients were identified through the computerised endoscopy database in SGH.

Definitions

Variceal bleeding

Variceal bleeding was defined as bleeding from an oesophageal or gastric varix at the time of endoscopy or the presence of large oesophageal varices with blood in the stomach and no other recognisable cause of bleeding[11].

Grading of oesophageal varices

Grade 1 oesophageal varices were defined as those that collapsed to insufflation of the oesophagus with air. Grade 3 oesophageal varices were those which were large enough to occlude the lumen and grade 2 oesophageal varices were those between grades 1 and 3[11].

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Corresponding Author: B S Yew, Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Road, Singapore 169608

Gastric varices
Gastric varices were divided into: (a) gastrooesophageal varices (GOV), which were associated with oesophageal varices; and (b) isolated gastric varices (IGV), which occurred independent of oesophageal varices. Type 1 GOV were continuous with oesophageal varices and extended for 2-5cm below the gastro-oesophageal junction along the lesser curvature of the stomach. Type 2 GOV extended beyond the gastrooesophageal junction into the fundus of the stomach. Type 1 IGV referred to varices that occurred in the fundus of the stomach and type 2 described varices anywhere in the stomach including the body, antrum, pylorus, and duodenum[11].

Time zero
Time zero was defined as the time of assessment of the patient at the Accident and Emergency (A&E) Department or Gastroenterology outpatient clinic or the time of first manifestation of variceal bleeding in patients whose bleeding occurred while in the hospital for other reasons.

Time frame of acute bleeding
The acute bleeding episode was represented by an interval of 48 hours from time zero with no evidence of clinically significant bleeding between 24 and 48 hours. Evidence of any bleeding after 48 hours was the first rebleeding episode[11].

Variceal rebleeding
Variceal rebleeding was defined as the occurrence of new haematemesis or melaena after a period of 24 hours or more from the 24 hour point of stable vital signs and haematocrit/haemoglobin following an episode of acute bleeding. All bleeding episodes regardless of severity should be counted in evaluating rebleeding[11].

Failure to control active bleeding
Failure to control bleeding was defined as one of the following, whichever occurred first:
(a) Fresh haematemesis more than or equal to two hours after the commencement of specific drug treatment or therapeutic endoscopy;
(b) Three gram drop in haemoglobin (approximately 9% drop in haematocrit) if no transfusion was administered;
(c) Death.
The time frame for failure to control bleeding after an acute bleeding episode was 120 hours (five days)[12].

Index bleed
For patients who had multiple hospitalisations for variceal bleeding during the study period, the first episode was considered as the index bleed.

Mortality
In-hospital mortality was defined as death occurring while hospitalised after the index bleed. Short-term mortality was death which occurred within six weeks after the index bleed. Overall mortality was death which occurred during the hospitalisation and during the follow-up till the study censor date of 30/9/05.

Data Collection
The case records of the patients were reviewed. The data collected comprised biodata, disease profile (aetiology, Child-Pugh score, previous variceal bleeding), laboratory data, endoscopic findings/therapy, time interval from A&E Department to oesophagogastroduodenoscopy (OGD), treatment details (antibiotics, vasoactive drugs, acid suppressant, use of blood products), hospital/intensive care unit stay, follow-up and outcome (rebleeding/death).

Statistical Analysis
The analysis was performed with Statistical Package for Social Sciences (SPSS) version 10.0 and the results were expressed as mean ± standard deviation unless otherwise stated.

RESULTS

Disease Profile
A total of 22 patients were eligible to be included in this study. The baseline characteristics of these patients are shown in Table I. Liver cirrhosis was the cause of varices in 21 (95.5%) patients. The remaining patient was a male patient who had non-cirrhotic portal hypertension. Chronic hepatitis B viral infection and alcohol were responsible for 38% (n=8) and 33% (n=7) of the liver cirrhosis respectively. Primary biliary cirrhosis, autoimmune cholangiopathy, autoimmune hepatitis, chronic hepatitis C viral infection, cryptogenic liver cirrhosis and Wilson's disease accounted for one case each. Just under half (48%, n=10) of the patients had Child's B liver cirrhosis. There were six patients (29%) with Child's A and five patients (24%) with Child's C liver cirrhosis respectively.

Five of the 22 patients (23%) had previous variceal bleeding. Three of these patients had oesophageal variceal bleeding and underwent variceal band ligation. The remaining two patients had gastric variceal bleeding and were treated with N-butyl-2-cyanoacrylate (Histoacryl) injections. All five patients received Propranolol as part of secondary prophylaxis. Twenty-one patients (95.5%) presented to the Department of A&E directly and the remaining patient (4.5%) was admitted through the Gastroenterology outpatient clinic.

Treatment details
The pharmacological and endoscopic treatments of acute variceal bleeding are shown in Table II. All 22 patients received antibiotics, vasoactive agents and acid suppressant. Intravenous Ceftriaxone and intravenous Metronidazole were the most commonly used antibiotics. Intravenous Somatostatin and intravenous Omeprazole were given to all patients. Overall, the patients required 2.4 ± 1.8 units of blood transfusion each.

All OGD were performed within a mean time of 11.1 ± 8.0 hours (range 1.8-26.8 hours). Twenty-one patients (95.5%) had oesophageal varices and two of these patients had concomitant gastric varices. The remaining one patient (4.5%) had only gastric varices. Oesophageal varices were the source of bleeding in 19 patients (86%). Gastric varices were the cause of bleeding in the remaining three patients (14%). All cases of bleeding oesophageal varices were treated with variceal band ligation and all bleeding gastric varices were injected with N-butyl-2-cyanoacrylate (Histoacryl). Grading of oesophageal varices was documented in 16 of the 21 patients who had oesophageal varices. There were 1, 10 and 5 patients with grade I, II and III oesophageal varices

Table I: Clinical and laboratory characteristics of patients

Total number of patients	22
Age (years)	54.8 ± 11.6
Gender (males/females)	17/5
Race, n (%)	
Chinese	18 (82%)
Malay	2 (9%)
Indian	2 (9%)
Cause of varices, n (%)	
Liver cirrhosis	21 (95.5%)
Non-portal hypertension	1 (4.5%)
Aetiology of liver cirrhosis, n (%)	
Chronic HBV infection	8 (38%)
Alcohol	7 (33%)
Primary biliary cirrhosis	1 (5%)
Autoimmune cholangiopathy	1 (5%)
Autoimmune hepatitis	1 (5%)
Chronic HCV infection	1 (5%)
Cryptogenic liver cirrhosis	1 (5%)
Wilson's disease	1 (5%)
Child-Pugh grade, n (%)	
A	6 (29%)
B	10 (48%)
C	5 (24%)
Child-Pugh score	8.1 ± 1.9
Previous variceal bleeding, n (%)	5 (23%)
Albumin (g/L)	26.4 ± 5.9
Bilirubin (mmol/L)	65.7 ± 85.5
Prothrombin time (sec)	14.6 ± 3.1
Haemoglobin (g/dL)	10.1 ± 2.8
Creatinine (mmol/L)	85.1 ± 32.3
Hepatocellular carcinoma, n (%)	6 (27%)

n= number of patients

Table II: Management and characteristics of acute variceal bleeding

Antibiotic, n (%)	
Ceftriaxone	20 (91%)
Metronidazole	15 (68%)
Cefepime	1 (4.5%)
Ampicillin sodium/ Sulbactam sodium (Unasyn)	1 (4.5%)
Vasoactive treatment, n (%)	
Somatostatin	22 (100%)
Acid suppressant, n (%)	
Omeprazole	22 (100%)
Blood products	
Blood transfusion (units)	2.4 ± 1.8
FFP (units)	1.8 ± 2.5
Platelets (units)	1.0 ± 2.2
Time from A&E Department to endoscopy (hours)	11.0 ± 8.0
Source of bleeding, n (%)	
OV	19 (86%)
GV	3 (14%)
Endoscopic therapy	
Bleeding OV	VBL (19 patients, 86%)
Bleeding GV	N-butyl-2-cryanoacrylate injection (3 patients, 14%)
Duration of stay in hospital	
ICU	0.1 ± 0.5
HD	2.3 ± 2.0
GW	5.5 ± 3.3

n= number of patients; FFP= fresh frozen plasma; A&E= accident and emergency;
OV= oesophageal varices; GV= gastric varices; VBL= variceal band ligation;
ICU= intensive care unit; HD= high dependency; GW= general ward.

respectively. However, grading of oesophageal varices was not available in five patients (24%). In addition, there was no documentation of the presence or absence of the red wale and white nipple signs in 82% (n=18) and 73% (n=16) of patients respectively.

Two of the three bleeding gastric varices were type I gastrooesophageal varices (GOV I) and the remaining one was type I isolated gastric varices (IGV I). None of these patients had concomitant oesophageal variceal bleeding.

The mean duration of the stay in the intensive care unit, high dependency unit and general ward were 0.1 ± 0.5, 2.3 ± 2.0 and 5.5 ± 3.3 days respectively.

Outcomes

Acute haemostasis was achieved in 21 patients (95.5%). Two patients (9%) died while in the hospital. One of these two patients (4.5%) had gastric variceal bleeding with failure to control the bleeding. The patient died as a result of bleeding gastric varices. The other patient died of hepatocellular carcinoma. This constituted an overall in-hospital mortality of 9%. There was no other death within six weeks of the index variceal bleed. The short-term mortality was thus 9%. Two other patients died during the follow-up (till the study censor date of 30/9/05). Both patients died of hepatocellular carcinoma. The overall mortality was 18%. Rebleeding occurred in four patients (18%). Three of the rebleeding was due to oesophageal varices and the remaining one was due to gastric varices. The time frame for rebleeding in our series ranged from 0.5 month to 14.6 months.

DISCUSSION

In our series of consecutive patients admitted to a tertiary center for variceal bleeding, the vast majority was consequent to liver cirrhosis. Amongst these patients, chronic hepatitis B viral infection was the main cause of liver cirrhosis. This is in keeping with local epidemiology. Chronic hepatitis B viral infection is of intermediate endemicity in Singapore and 4% of the population in Singapore have chronic hepatitis B viral infection. On the other hand, chronic hepatitis C viral infection is relatively uncommon in Singapore. Only one patient in this cohort had non-cirrhotic portal hypertension.

The in-hospital mortality rate and the overall rebleeding rate in our series were 9% and 18% respectively. These figures are relatively low compared to published data. The in-hospital mortality rate was in the order of 14% in recent studies[8,9]. The rebleeding rate during the follow-up period in the study conducted by Chalasani *et al*[8] was 29%. We postulate the following reasons to explain the differences. Firstly, the two aforementioned studies[8,9] had a higher proportion of patients with more severe liver dysfunction. Thirty-six percent and 45% of the patients in the studies conducted by Chalasani et al8 and Carbonell *et al* (year 2000 cohort)[9] had Child's C liver cirrhosis respectively. In contrast, 24% of the patients in our series had Child's C liver cirrhosis. Secondly, all patients in our series received pharmacological and endoscopic treatments as recommended by major guidelines and consensus[3,11-13]. All patients received antibiotics and vasoactive treatment. Up to 20% of cirrhotic patients who are hospitalised for gastrointestinal bleeding have bacterial infections[11,14]. It has been demonstrated that bacterial infections significantly increase the risk of failure to control bleeding, rebleeding and mortality in this group of patients[15]. Vasoactive drugs can be used to reduce portal pressure and have been shown to be effective in controlling variceal bleeding[13]. Terlipressin, Somatostatin, Octreotide and Vasopressin with Nitroglycerin may be used in the treatment of variceal bleeding[3]. It is recommended that one of the vasoactive drugs should be started as soon as possible (before endoscopy) and be maintained for 2 to 5 days in patients with oesophageal variceal bleeding[3,12]. All patients in our series were commenced on intravenous Somatostatin upon admission.

Oesophagogastroduodenoscopy should be performed within 12 hours after admission, especially in patients with significant bleeding[3,12]. For our patients, the mean time from the A&E Department to endoscopy was within this recommended time frame. We were unable to compare this with the earlier studies as these data were not available.

The outcome of acute variceal bleeding in patients with cirrhosis has clearly improved in the past decades. This could be explained by the introduction and combination of the various therapies. Somatostatin, terlipressin, endoscopic sclerotherapy, endoscopic banding, transjugular intrahepatic portosystemic shunt, advances in surgical techniques, advances in intensive care, and the recognition of the importance of bacterial infection have all played a role in improving the prognosis of variceal bleeding. Endoscopic variceal ligation achieves haemostasis in 90% of patients. It is superior to sclerotherapy in terms of efficacy and safety[3,14]. In our series, all patients (n=19) with oesophageal variceal bleeding were treated with variceal band ligation and acute haemostasis was achieved in all cases. Three of these patients subsequently suffered from rebleeding and the time frame ranged from 6.9 month to 14.6 months. The rebleeding was successfully controlled with a repeat variceal band ligation.

Our study has identified an area of deficiency in the documentation of endoscopic findings. Oesophageal variceal grading was absent in 24% (n=5) of patients and there was no documentation of either the red wale sign or the white nipple sign in up to 82% patients. The importance of such documentations should be further emphasised to the endoscopists as it will certainly facilitate the continuation of care.

In conclusion, the relatively low in-hospital mortality and rebleeding rates in our series are likely to be due to the smaller proportion of patients with severe liver dysfunction and management which adhered to recommendations. However, there is room for improvement in the documentation of endoscopic findings in a significant proportion of patients.

REFERENCES

1. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut 2002; 51(Suppl IV): iv1-iv6.
2. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and oesophageal varices. A prospective multicentre study. The North

Italian Endoscopic Club for the Study and Treatment of Oesophageal Varices. N Engl J Med 1988; 319: 983-9.
3. Bosch J, Abraldes JG, Groszmann R. Current management of portal hypertension. J Hepatol 2003; 38(Suppl 1): S54-S68.
4. Franchis RD, Primignani M. Natural history of portal hypertension in patients with cirrhosis. Clin Liver Dis 2001; 5: 645-63.
5. McCormick PA, O'Keefe C. Improving prognosis following a first variceal haemorrhage over four decades. Gut 2001; 49: 682-5.
6. El-Serag HB, Everhart JE. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. Am J Gastroenterol 2000; 95: 3566-73.
7. Gunnarsdottir SA, Olsson R, Bjornsson ES. Characteristics, prognosis and outcome of patients with oesophageal varices in a university hospital in Sweden 1994-1999. Scand J Gastroenterol 2005; 40: 1462-8.
8. Chalasani N, Kahi C, Francois F, *et al.* Improved patient survival after acute variceal bleeding: a multicentre, cohort study. Am J Gastroenterol 2003; 98: 653-9.
9. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004; 40: 652-9.
10. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. Lancet 2003; 361: 952-4.
11. Jalan R, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology. Gut 2000; 46(Suppl III): iii1-iii15.
12. Franchis RD. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43: 167-76.
13. Lebrec D, Vinel JP, Dupas JL. Complications of portal hypertension in adults: a French consensus. Eur J Gastroenterol Hepatol 2005; 17: 403-10.
14. Comar KM, Sanyal AJ. Portal hypertensive bleeding. Gastroenterol Clin North Am 2003; 32: 1079-105.
15. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal haemorrhage. Hepatology 1998; 27: 1207-12.