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BRIEF ARTICLE

Variceal hemorrhage: Saudi tertiary center experience of clinical presentations, complications and mortality

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Abstract

AIM: To determine the clinical presentation, underlying etiology and short- and long-term outcomes of acute variceal bleeding (AVB).

METHODS: A retrospective descriptive cohort study of cirrhotic patients with AVB who were admitted to King Abdul Aziz University Hospital between January 2005 and December 2009. We obtained demographic data for all patients. For each patient we also obtained the clinical data at presentation; cause of liver cirrhosis, bleeding presentation (hematemesis and/or melena), presence of ascites, hepatic encephalopathy and renal impairment (RI) or hepatorenal syndrome. We carried out complete blood count, prothrombin time evaluation, and liver function tests. We also report all episodes of re-bleeding after the first episode of AVB, both during the initial admission and after discharge. We recorded the length of stay for each patient and thereby calculated the mean duration of stay for all patients. The length of follow-up after the first AVB and the outcome for each patient at the end of the study period were recorded. Causes of mortality either related to liver disease or non-liver disease cause were determined.

RESULTS: A 125 patients were enrolled in the study. The number of episodes of AVB for each patients varied between 1 and 10. Survival from the first attack of AVB to death was 20.38 mo (SD 30.86), while the length of follow-up for the living patients was 53.58 mo (SD 24.94). Total number of AVB admissions was 241. Chronic hepatitis C, the commonest underlying etiology for liver disease, was present in 46 (36.8%) patients. Only 35 (28%) patients had received a primary prophylactic β-blocker before the first bleeding episode. The mean hemoglobin level at the time of admission was 8.59 g/dL (SD 2.53). Most patients had Child-Pugh Class C 41 (32.8%) or Class B 72 (57.6%) disease. Hematemesis was the predominant symptom and was found in 119 (95.2%) patients, followed by melena in 75 (60.0%) patients. Ascites of variable extent was documented in 93 (74.4%) patients. We identified hepatic encephalopathy in 31 (28.8%) patients and spontaneous bacterial peritonitis in 17 (13.6%). Bleeding gastric varices was the cause of AVB in 2 patients. AVB was associated with shock in 22 patients, 13 of whom (59.1%) had Child-Pugh class C disease. RI was noted in 19 (46.3%) of 41 patients in Child-Pugh class C and 14 (19.4%) of 72 patients in Child-Pugh class B. None of the patients with Child-Pugh class A disease had RI. Emergency endoscopy was effective in controlling the bleeding, although the re-bleeding rate was still high, 12 (9.6%) during the same admission and 55 (44%) after discharge. The re-bleeding rate was higher in patients with ascites, occurring in 40/55 (72.2%). The length of hospital stay was 1-54 d with a mean of 8.7 d. Three patients had emergency surgery due to failure of endoscopic treatment and balloon tamponade. The overall long term mortality was 65%. Survival from the first attack of AVB to death was 20.38 ± 30.86 mo, while the length of follow-up for the living patients was 53.58 ± 24.94 mo. Patients with Child-Pugh score C had a higher risk of liver disease-related mortality

(67.6%). RI (developed during admission) was the main factor that was associated with mortality (P = 0.045).

CONCLUSION: The majority of patients with liver disease who present at the emergency unit for AVB are at an advanced stage of the disease. The outcome is poorer for patients who develop RI during hospitalization.

Key words: Endoscopy; Liver disease; Mortality; Outcome; Varices; Variceal bleeding

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INTRODUCTION

Variceal bleeding is a leading cause of mortality and morbidity in patients with liver cirrhosis of various causes[1]. Varices and variceal bleeding can develop during both the early or late stages of cirrhosis (from Child-Pugh A to C)[2]. It has been reported that about half of cirrhotic patients will develop varices due to portal hypertension and 40% of them will have variceal bleeding[3,4]. A variety of non-invasive factors have been linked to the development of varices in cirrhotic patients. These include platelet counts, portal vein diameter, the size of the spleen and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio[5-7]. Similarly, several reports have addressed the use of non-invasive parameters to predict the presence of large esophageal varices with a high chance of bleeding. Those parameters most frequently include low platelet counts, splenomegaly, prothrombin time, ascites and advanced Child-Pugh class[8-11].

The gold standard test for the diagnosis of varices is upper gastrointestinal endoscopic examination (OGD). Hence, routine screening by OGD is recommended for all cirrhotic patients[12]. Once large varices are diagnosed, primary prophylactic measures for prevention of the first bleeding episode are recommended[12]. Selective β-blockers such as propranolol have been the most frequently used and studied agents for medical primary prophylaxis[12,13]. Variceal band ligation has been also used as prophylaxis for the prevention of variceal bleeding, and shows less frequent bleeding episodes than medical prophylaxis. However, there is no significant difference in mortality[14,15].

In Saudi Arabia, only a few studies have reported the clinical outcomes of patients with acute variceal bleeding (AVB)[16-18]. In this retrospective analysis, we reviewed the medical data of patients with AVB who were admitted to King Abdul Aziz University Hospital (KAUH), Jeddah, Saudi Arabia, to determine the clinical presentation, common underlying etiology and short- and long-term outcomes of the bleeding in this group of patients.

MATERIALS AND METHODS

Study population

We conducted a retrospective descriptive cohort study of all patients with upper gastrointestinal bleeding due to AVB who were admitted to KAUH, Jeddah, Saudi Arabia between January 2005 and December 2009. Ethical approval for the study was granted by the Biomedical Ethics Research Committee of King Abdul Aziz University.

We included all patients with AVB due to underlying liver cirrhosis who had undergone emergency endoscopic intervention. We excluded elective admission episodes for variceal band ligation after acute bleeding in the same patients. For all cases included in the study, we collected the following information: age, gender, nationality, use of a primary prophylactic β-blocker (propranolol) before the first episode of variceal bleeding, clinical data on the first episode of AVB, cause of liver disease, presence of hematemesis and/or melena and the duration of symptoms. We also recorded the presence of ascites (whether none, mild, moderate or massive) and evidence of spontaneous bacterial peritonitis (SBP), as reflected by fever and abdominal pain and ascitic fluid analysis for cell count. The presence of hepatic encephalopathy on admission was also noted. We looked for the presence of hemodynamic instability by measuring blood pressure and pulse rate at the time of presentation to the emergency department. For patients who had more than one episode of AVB, we recorded the number of episodes.

We conducted the following laboratory tests: complete blood count at the time of admission; prothrombin time to assess the Child-Pugh score on admission; and liver function tests, namely serum ALT, AST, alkaline phosphatase, γ-glutamyl transferase, total protein, albumin, total and direct bilirubin. Our management for all patients with AVB includes standard resuscitation measures in addition to the use of intravenous vasoconstrictors, such as Octreotide, followed by endoscopic therapy. In patients who had severe acute bleeding that obscured the field and caused failure of immediate band ligation, balloon tamponade was used and endoscopic banding was then performed within the next 48 h. In addition to this, and as per the American Association for the Study of Liver Diseases recommendation, all patients managed for AVB at our institution receive short-term prophylactic antibiotics during hospitalization[2].

The presence of renal impairment (RI) or hepatorenal syndrome at presentation or during admission for

AVB was recorded. We define in-hospital re-bleeding as recurrence of variceal bleeding during the admission after initial control and late re-bleeding- as recurrent variceal bleeding between 6 wk and 6 mo after discharge from the hospital. The length of hospital stay for each patient during the admission was also recorded. The duration of follow-up after the first episode of variceal bleeding and the outcome of each patient at the end of the study period were recorded. The cause of mortality during the follow up was noted as being due to either liver disease or non-liver disease.

Statistical analysis

We performed statistical analysis using the SPSS Version 15. χ^2 test was used to assess the relation between the Child-Pugh score and the risk of bleeding and mortality. The relation between the severity of bleeding and the Child-Pugh score was also assessed by the χ^2 test. Descriptive statistics was used to determine mortality. Multivariate analysis was used to assess the risk factors associated with mortality.

RESULTS

Baseline characteristics

One hundred twenty-five patients were enrolled in the study. The number of admissions was 1-10 per patient with a total of 241 admissions (Table 1). Only 35 (28.0%) patients had a history of β-blocker use. Ten (8.0%) had Child-Pugh class A disease, 72 (57.6%) had Child-Pugh class B, and 41 (32.8%) had Child-Pugh class C. The Child-Pugh score was not determined for 2 patients. Patients in Child-Pugh class A had no previous evidence of liver cirrhosis. The most common cause of liver disease was chronic hepatitis C (n = 46, 36.8%) followed by non alcoholic fatty liver disease (n = 26, 20.8%). For six patients, the cause of liver disease was not determined during admission and the patients were lost to follow up after the initial admission. Hematemesis was a presenting symptom in the majority of the cases (n = 119, 95.2%), while melena was noted in 75 (60.0%) patients. Fever was uncommon, noted in 15 (12.0%) of the patients, and abdominal pain was seen in only 13 (10.4%) of the cases. The presence or absence of ascites was documented in 123 patients. There was no ascites in 30 (24.0%) patients, 46 (36.8%) had mild ascites, 32 (25.6%) had moderate ascites and 15 (12%) had massive ascites. Hepatic encephalopathy was present in 31 (24.8%) patients on admission, and SBP was diagnosed in 17 (13.6%) patients.

The results of baseline laboratory investigations are summarized in (Table 2). All patients from our cohort underwent diagnostic and therapeutic emergency endoscopy within 12 h of admission after the baseline standard measures for AVB. Two patients who had bleeding gastric varices had optimal response to cyanoacrylate injection.

Relationship between the clinical variables

The bleeding was more severe in patients with ascites; 20 (90.9%) of 22 patients who had shock at presentation had ascites. Thirteen (59.1%) of these 22 were Child-Pugh C. Thirty-three (26.4%) patients developed RI during hospitalization. Amongst the patients in Child-Pugh class C, 19 of 41 patients (46.3%) developed renal failure. RI was noted in 14 (19.4%) of 72 patients in Child-Pugh class B, while no case of renal failure was observed in patients in Child-Pugh class A. Based on the degree of ascites, RI was noted in 11 patients with massive ascites, in 9 patients with moderate ascites, and in 10 patients with mild ascites. Only 3 patients without ascites developed RI. In-hospital re-bleeding was recorded in 12 (9.6%) patients and late re-bleeding in 55 (44.0%) patients. Patients who had ascites were more likely to have a re-bleeding episode; they accounted for 40 of 55 (72.2%) patients with re-bleeding.

Table 1 Number of emergency admissions *n* (%)

No. of episodes of acute variceal bleeding	No. of patients
1	70 (56.0)
2	27 (21.6)
3	15 (12.0)
4	5 (4.0)
5	1 (0.8)
6	5 (4.0)
7	1 (0.8)
10	1 (0.8)
Total	125 (100)

Relationship between the length of hospital stay and severity of ascites and renal failure

The length of hospital stay varied between 1 and 54 d (mean ± SD, 8.7 ± 7.9 d). Length of stay was longer for patients who had massive ascites when compared with those who had mild, moderate or no ascites, but the difference was only statistically significant between patients with massive ascites and those with mild ascites (P = 0.036).

Three patients had emergency devascularization surgery for refractory variceal bleeding; one of them had a huge gastric varix.

Survival and mortality

The survival period from the first attack of AVB to death was 20.38 ± 30.86 mo. The length of follow-up for the living patients was 53.58 ± 24.94 mo. Amongst the 60 patients who were available for follow up, 37 (61.7%) died from complications due to liver disease after a mean of 20.38 ± 30.86 mo, while the cause of death was unrelated to the underlying liver disease in 2 (3.3%) cases. The overall mortality was 65%. Patients with Child-Pugh score C had a higher risk of liver disease-related mortality. Twenty-five (67.6%) of the 37 patients who died were Child-Pugh class C. Patients who had ascites also had a higher risk of mortality related to liver disease; 34 of 37 (91.9%). Four of the patients who had SBP were lost to follow-up, while 11 of the remaining 13 patients died of

Table 2 Mean and SD of the laboratory results of all patients at the time of first admission

Investigation	Minimum	Maximum	mean (SD)	Reference range
CBC				
White cell count (K/μL)	1.8	28.10	8.27 (5.12)	3-11
Hemoglobin (g/dL)	1.0	15.70	8.59 (2.53)	12-17
Platelets (K/μL)	24.0	463.00	133.89 (85.63)	100-400
ALT (U/L)	13.0	759.0	75.73 (84.93)	30-65
AST (U/L)	12.0	631.0	90.62 (106.2)	15-37
Albumin (g/L)	10.0	37.0	24.71 (5.88)	35-50
Bilirubin (μmol/L)	5.0	473.0	37.12 (51.82)	0-17
Alkaline phosphate (U/L)	17.0	561.0	141.31 (83.10)	50-136
GGT (U/L)	14.0	889.0	132.03 (143.48)	5-85
Total protein (g/L)	40.0	87.0	64.37 (10.95)	64-82
Prothrombin time (s)	11.2	141.0	18.86 (14.80)	10-14

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CBC: Complete blood count; GGT: γ glutamyl trasferase.

liver disease. On multiple regression analysis, RI (developed during admission) was the only factor that was significantly associated with mortality ($P = 0.045$).

Mortality during the first admission was reported in 19 (15.2%) patients, all the remaining patients had follow-up elective band ligation at 3-4 wk intervals until eradication of the varices was achieved [21 patients (16.8%)] or until the patient died [20 (16%)] or lost from the follow-up [65 (52%)].

DISCUSSION

The results of this study show that chronic hepatitis C was the most common cause of liver disease in patients who presented with AVB at the emergency department of KAUH. On admission, the majority of the patients were in Child-Pugh class B and C, and severe variceal bleeding was greater in patients with advanced disease (Child-Pugh class C). Mortality was related to the underlying cause of the disease in 37 of 39 patients who died, while the cause was not related to the underlying liver disease in the remaining two patients. RI, developed during the course of hospitalization, was the only factor that was significantly associated with mortality.

Hematemesis was the presenting symptom in up to 95.2% of our study population. Melena was present in 50.0%, while abdominal pain was an infrequent symptom, observed in only 10.4% of the cases. It was reported that many patients with large varices are asymptomatic, and variceal rupture with massive upper gastrointestinal hemorrhage can sometimes be the first presenting symptom in patients with liver cirrhosis[19]. This was probably the case in patients with stable Child-Pugh class A disease from our cohort. On the other hand, patients with advanced liver disease and Child-Pugh class C have a higher risk of variceal bleeding and poorer outcome compared with patients who have Child-Pugh class A disease and compensated cirrhosis[19], as was the case in our study.

The main factor that predicts the severity of variceal bleeding is intravariceal pressure, and the level of bleeding could vary from moderate to life-threatening massive hemorrhage with shock[20,21]. Ascites has been reported as a predictor of the severity of AVB[22]. The fact that the bleeding was more severe in our patients with ascites could be due to an elevated portal vein pressure as a result of increased intra-abdominal pressure.

The initial management of AVB includes standard resuscitation measures in addition to the use of intravenous vasoconstrictors, such as Octreotide, followed by endoscopic therapy[20-24]. This will control the bleeding in the majority of patients. However, in cases where the bleeding is not controlled by initial measures, emergency transjugular intrahepatic portosystemic shunt is the best alternative in those who can tolerate the procedure[20,21,23]. Only 3 of our patients had emergency surgery for refractory variceal bleeding. Immediate liver transplantation may be considered if possible in appropriate candidates[21,23,25]. Repeated endoscopic management until complete obliteration is achieved is recommended for patients who responded to this procedure[20,21]. The addition of β-blockers as secondary prophylaxis has been shown in several reports to be superior to the use endoscopic management alone[21,26]. All of our patients had β-blockers as secondary prophylaxis and none of them experienced serious side effects. In cases of acute gastric variceal bleeding, cyanoacrylate injection has been also tried for secondary prophylaxis and shown to be superior to β-blockers[27]. It was used effectively in two patients from our cohort who had gastric varices. New modalities for secondary prevention of re-bleeding, including microwave coagulation, have also been studied and shown to be effective[26].

In this study, in-hospital re-bleeding was observed in about 9.6% of the cases while nearly half of the patients had recurrent variceal bleeding after discharge. Other authors reported a similar rate of early re-bleeding in patients who underwent endoscopic therapy for AVB. The rate of re-bleeding in their study was between 9% and 19%[28]. In a recent study, the authors found that the predictors of early re-bleeding were moderate to excessive ascites, the number of bands placed during endoscopic band ligation, the extent of varices, and the prothrombin time. They went further and demonstrated that a moderate to excessive volume of ascites was the most impor-

tant factor predicting variceal bleeding following endoscopic variceal ligation[29]. Other factors that have been associated with high mortality and re-bleeding following AVB are the presence of hepatocellular carcinoma and bacterial infection at the time of bleeding[29,30].

The overall mortality in this study was 65%, higher than the 19% reported by other authors in a large study conducted at a tertiary hospital in Riyadh[18]. In other studies conducted abroad, the rate of mortality is at least 20% at 6 wk in patients with AVB[31,32]. The high mortality rate in our study could be related to the presence of advanced liver disease in many patients. We found that patients in Child-Pugh class C, SBP and ascites presented a higher risk of dying due to liver disease, although RI, developed during hospitalization, was the sole factor that was significantly related to mortality.

In conclusion, most patients with liver disease that present at the emergency unit for AVB are at an advanced stage of the disease. Endoscopy is a reliable method to control the bleeding, but it is associated with a high rate of late re-bleeding. Hence, close follow up is necessary in patients who have undergone this procedure for bleeding varices. The outcome is poorer for patients who develop RI during hospitalization, and the principal of clinicians should not be on the bleeding alone but measures should also be taken to prevent the occurrence of complications during hospitalization. Emphasis on endoscopic screening of patients who have liver cirrhosis for the presence of varices and early implementation of primary prophylaxis will help to reduce the chance of variceal bleeding and its complications.

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COMMENTS

Background

Acute variceal bleeding (AVB) is a major cause of morbidity and mortality in patient with liver cirrhosis. About half of cirrhotic patients especially those with advance disease will develop esophageal varices and variceal bleeding. Researchers and experts from different regions of the world have been working to improve therapeutic techniques and medical care practice in AVB to achieve better outcomes. Similarly the world major associations for liver disease are continuously updating the clinical data and practice guideline for the management of AVB. However there are only limited data from the Middle East and Arab world in this field. Hence, studies from this part of the world will reflect the local clinical data and outcomes of such patients and may show possible differences from other international figures.

Research frontiers

The focus of this clinical study was to define the clinical outcomes, complications and mortality risk factors of acute variceal hemorrhage at King Abdul Aziz University (KAUH) hospital, a major teaching hospital and tertiary care center in the region. KAUH receives large numbers both Saudi and non-Saudi patients

Innovations and breakthroughs

Most breakthroughs in AVB have been in the field of AVB management. Several international guidelines have been suggested by major liver associations, such as American Association for the Study of Liver Diseases (http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Prevention%20and%20Management%20of%20Gastro%20Varices%20and%20Hemorrhage.pdf), EASL and the APASL. The introduction of TIPS and early surgical intervention in the management of variceal bleeding has led to significant improvement in patient outcomes.

Applications

The study has shown that development of renal impairment or hepatorenal syndrome are associated with a high chance of mortality. Future prospective studies on similar patients with early initiation of preventive measures for renal failure, such as albumin infusion with or without terlipressin, might lead to reduction in the mortality rate of patients with AVB.

Peer review

The manuscript describes the outcomes of variceal bleeding and band ligation in a series of 125 patients. A variety of outcomes and parameters are described. Only 50% of patients were followed up for mortality analysis and this seems to be more the case for patients in Childs C than other patients.

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