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ORIGINAL ARTICLE

Prospective Study

Mortality and rebleeding following variceal haemorrhage in liver cirrhosis and periportal fibrosis

Sara Elfadil Abbas Mohammed, Abdelmunem Eltayeb Abdo, Hatim Mohamed Yousif Mudawi

Sara Elfadil Abbas Mohammed, Hatim Mohamed Yousif Mudawi, Department of Internal Medicine, Faculty of Medicine, University of Khartoum, Khartoum 11111, Sudan

Abdelmunem Eltayeb Abdo, National Centre for Gastro-intestinal and Liver Disease, Ibn Sina specialized Hospital, Khartoum 11111, Sudan

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Correspondence to: Hatim Mohamed Yousif Mudawi, FRCP, Professor, Department of Internal Medicine, Faculty of Medicine, University of Khartoum, PO Box 2245, Khartoum 11111, Sudan. hmudawi@hotmail.com
Telephone: +249-91-2202600
Fax: +249-15-5117877

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Abstract

AIM

To investigate mortality and rebleeding rate and identify associated risk factors at 6 wk and 5 d following acute variceal haemorrhage in patients with liver cirrhosis and schistosomal periportal fibrosis.

METHODS

This is a prospective study conducted during the period from March to December 2014. Patients with portal hypertension presenting with acute variceal haemorrhage secondary to either liver cirrhosis (group A) or schistosomal periportal fibroses (group B) presenting within 24 h of the onset of the bleeding were enrolled in the study and followed for a period of 6 wk. Analysis of data was done by Microsoft Excel and comparison between groups was done by Statistical Package of Social Sciences version 20 to calculate means and find the levels of statistical differences and define the mortality rates, the *P* value of < 0.05 was considered to be significant.

RESULTS

A total of 94 patients were enrolled in the study. Thirty-two patients (34%) had liver cirrhosis (group A) and

62 (66%) patients had periportal fibrosis (group B). Mortality: The 6-wk and 5-d mortality were 53% and 16% respectively in group A compared to 10% and 0% in group B (*P* value < 0.000 and < 0.004). In group A; a Child-Turcotte-Pugh class C and rebleeding within 5 d were significantly associated with 5-d mortality (*P* value < 0.029 and < 0.049 respectively) and Child- Turcotte-Pugh class C was also a significant risk factor for 6-wk mortality (*P* value < 0.018). In group B; mortality was significantly associated with rebleeding within the 6-wk follow-up period and requirement for blood transfusion on admission (*P* value < 0.005 and < 0.049). Rebleeding: The 6-wk and 5-d rebleeding rate in group A were 56% and 25% respectively compared to 32% and 3% in group B (*P* value < 0.015 and < 0.002). Clinical presentation with encephalopathy was a significant risk factor for 5 d rebleeding in group A (*P* value < 0.005) while grade Ⅲ periportal fibrosis and requirement for blood transfusion on admission were significant risk factors for 6-wk rebleeding in group B (*P* value < 0.004 and < 0.02).

CONCLUSION

The 6-wk and 5-d mortality and rebleeding rate were significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

Key words: Variceal haemorrhage; Periportal fibrosis; Liver cirrhosis; Mortality; Rebleeding

Core tip: This study was conducted to investigate the rate and risk factors associated with rebleeding and mortality at 6 wk and 5 d following acute variceal haemorrhage in patients with liver cirrhosis and schistosomal periportal fibrosis (PPF). The 6-wk and 5-d mortality in cirrhosis were 56% and 16% compared to 10% and 0% in patients with schistosomal PPF (*P* value < 0.000 and < 0.004). The 6-wk and 5-d rebleeding rate in cirrhosis were also high at 53% and 25% compared to 32% and 3% respectively in patients with schistosomal PPF (*P* value < 0.015 and < 0.002). In conclusion the 6-wk and 5-d mortality and rebleeding were significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

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INTRODUCTION

Variceal bleeding is a devastating complication of portal hypertension. The 6-wk mortality in patients with liver cirrhosis is between 17%-28%[1-3] and the risk of rebleeding after acute variceal haemorrhage (AVH) is highest within the first 6 wk with a peak in the first 5 d[2]. In Sudan, a country endemic with schistosomiasis, AVH in the majority of cases is caused by portal hypertension due to schistosomal periportal fibrosis (PPF), while cirrhosis is less common[4]. Published data from Sudan showed that the crude mortality rate of schistosomiasis in a village in the Gezira state; an area endemic for schistosomiasis was 51/100000 per year with a case fatality per year of 1/1000 in those secreting eggs and 11/100 in those with bleeding varices[5]. Significant risk factors for variceal bleeding in patients with schistosomal portal hypertension, after at least one episode of bleeding compared to patients with schistosomal PPF without bleeding were splenic longitudinal dimension of more than 11 cm and PPF of ≥ grade Ⅲ[6]. The 6-wk and 5-d mortality and rebleeding rate following AVH in schistosomal portal hypertension have not been well studied.

The objectives of this study were to investigate mortality and rebleeding rate and identify associated risk factors for 6 wk and 5 d following acute variceal haemorrhage in patients with portal hypertension secondary to liver cirrhosis and schistosomal PPF.

MATERIALS AND METHODS

This is a prospective study conducted at Mohamed Salih Idris bleeding centre in Khartoum state, Sudan from March to December 2014. Patients presenting with acute upper gastrointestinal (GI) bleeding, whether it was their first bleeding episode or otherwise, were included if they were > 16 years old, had portal hypertensive variceal bleeding (diagnosed on upper gastrointestinal endoscopy) secondary to liver cirrhosis (group A) or PPF (group B) presenting within 24 h of the onset of the bleeding. Patients were excluded if they were ≤ 16 years, had hepatocellular carcinoma or had non variceal upper gastrointestinal bleeding. Data were collected in a specially designed sheet which included patients' demographics and clinical presentation, baseline laboratory tests done upon initial presentation (CBC, RFT, LFT's and INR), patients' hemodynamic status upon presentation, the number of blood units transfused, the amount of the vasopressor agent Terlipressin acetate (Glypressin®, Ferring, Germany) used, endoscopic findings and endoscopic management done. All patients received Terlipressin 2 mg intravenously bolus dose followed by 1 mg 6 hourly whenever the drug was available. All patients underwent upper gastrointestinal endoscopy within 12 h of admission to identify the source of bleeding. Oesophageal varices were graded according to Paquet[7] and gastric varices were graded according to Sarin *et al*[8]. Oesophageal varices and junctional varices (GOV1) were treated with injection sclerotherapy or band ligation, whichever was available, 5% ethanolamine oleate was the agent used for injection sclerotherapy and the volume used for each patient was documented, junctional varices (GOV2) and isolated gastric varices

Table 1 Demographic criteria and clinical presentation in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)

Variable	PPF (*n* = 62)	Cirrhosis (*n* = 32)	*P* value
Males	56 (90.3)	27 (84.4)	0.395
Females	6 (9.7)	5 (15.6)	
Mean age (yr)	49.3 ± 13.4	48.7 ± 15.1	0.840
HBV	4 (6.5)	8 (25)	0.004[1]
HCV	2 (3.2)	1 (3)	
HBV and HCV	0 (0)	3 (9.4)	
SBP > 100, PR < 100	50 (80.6)	18 (56.2)	0.012[1]
SBP < 100, PR > 100	12 (19.4)	14 (43.8)	
Hb < 5 g/dL	10 (16.1)	4 (12.5)	0.236
Hb 5-10 g/dL	36 (58.1)	24 (75)	
Hb > 10 g/dL	16 (25.8)	4 (12.5)	

[1]Significant risk factor. HBV: Hepatitis B virus; HCV: Hepatitis C virus; SBP: Systolic blood pressure; PR: Pulse rate; Hb: Haemoglobin.

were treated with the injection of cyanoacrylate (Histoacryl®, B Braun, Spain) and Sengstaken Blakemore tube was used to control bleeding if initial endoscopy was not successful. Cirrhotic patients were covered with prophylactic antibiotics. An appointment for secondary prophylactic endoscopic treatment was given within 2 wk and B-blockers were prescribed if not contraindicated. The diagnosis of cirrhosis was established by clinical, radiological and laboratory findings and the cause of cirrhosis was looked for and documented. Child-Turcotte-Pugh (CTP) classification and the model for end stage liver disease (MELD) score were calculated for each patient. In the case of schistosomal PPF, the severity of liver fibrosis was graded as described by Homeida *et al*[9] from Ⅰ-Ⅲ as follows: Grade Ⅰ: Mild echogenic thickening of one or two portal vein radicles with little change in the walls of the portal vein; Grade Ⅱ: Moderate to severe periportal irregular thickening of most of the portal vein radicles, with marked narrowing of the central lucency, marked thickening at the bifurcation of the portal vein, and mild thickening of the main portal vein; and Grade Ⅲ: Marked thickening of the walls of the portal vein radicles with obliteration of the central lucency in the peripheral branches forming thick irregular echogenic 10-20 mm bands reaching the periphery of the liver with thickening down to main portal vein walls.

Patients were followed every 24 h for the first 5 d and then at 6 wk for mortality and rebleeding. Rebleeding was defined according to the Baveno V consensus as a single episode of clinically significant rebleeding from portal hypertensive sources (recurrent melena, hematemesis resulting in hospital admission, blood transfusion, 3 g drop in haemoglobin or death). Rebleeding during the first 120 h (5 d) was regarded as treatment failure, whereas rebleeding up to 6 wk was regarded as failure of secondary prophylaxis[10].

The primary endpoint of this study was the rate of variceal rebleeding and mortality at 5 d and at 6 wk following AVH in portal hypertension secondary to cirrhosis or PPF. The secondary endpoints were to determine risk factors associated with variceal rebleeding and mortality at 5 d and 6 wk among the study population.

The study was reviewed and approved by the Research and Ethics Review Committee at Mohamed Salih Idris Centre. All study participants or their legal guardian provided their informed consent before being enrolled in the study.

Statistical analysis

Analysis of data was done by Microsoft Excel and comparison between groups was done by Statistical Package of Social Sciences version 20 to calculate means and find the levels of statistical differences and define the mortality rates, the *P* value of < 0.05 was considered to be significant.

RESULTS

A total of 94 patients were enrolled in the study with a mean age of 49 ± 1.0 years, and males constituted 88% with M:F ratio of 7:1.

Group A (liver cirrhosis)

There were 32 patients (34%) in group A. Demographic criteria and clinical presentation are shown in Table 1, clinical findings and medical management in Table 2 and endoscopic findings/management are shown in Table 3. After discharge from the bleeding centre, patients were advised to attend for further endoscopic management in order to eradicate the varices with the earliest session to be done at 2 wk. A total of 19% underwent upper endoscopy at less than 2 wk because of rebleeding, 31% performed the session at the advised 2 wk, 13% at 3 wk, 3% at 4 wk and 3% beyond 4 wk, whereas 31% did not attend for the second endoscopy session.

Group B (schistosomal PPF)

There were 62 patients (66%) in group B. The clinical and demographic data are shown in Table 1, ultrasound findings and medical management in Table 2 and endoscopic findings/management are presented in Table 3.

After discharge from the bleeding centre patients were advised to continue endoscopic management in order to eradicate the varices with the earliest session to be done at 2 wk. A total of 5% of the patients underwent upper endoscopy at less than 2 wk because of rebleeding, 48% performed the session at the advised 2 wk, 23% at 3 wk, 8% at 4 wk and 11% beyond 4 wk while 5% did not attend for the second endoscopy session.

Overall mortality

The 6-wk and 5-d mortality were 53% and 16% respectively in group A compared to 10% and 0% in group B (*P* value < 0.000 and < 0.004 respectively) (Table 4).

Factors related to mortality

In group A, the CTP class C and rebleeding within 5 d were significant risk factors for 5 d mortality (*P* value < 0.029 and < 0.049 respectively). CTP class C was also

Table 2 Clinical findings and medical management provided in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)

Variable	PPF (*n* = 62)	Cirrhosis (*n* = 32)	*P* value
Jaundice	0 (0)	16 (50)	0.000[1]
Ascites	5 (8.1)	16 (50)	0.000[1]
Encephalopathy	3 (4.8)	9 (28.1)	0.001[1]
Child class A	-	9 (28)	-
Child class B	-	13 (41)	-
Child class C	-	10 (31)	-
MELD score < 18		19 (59.4)	-
MELD score > 18		13 (40.6)	-
PPF grade Ⅱ	29	-	-
PPF grade Ⅲ	71	-	-
Mean portal vein diameter	17.4 ± 3.3 mm	16.4 ± 3.1 mm	0.155
Terlipressin stat dose 2 mg Ⅳ	48 (77.4)	27 (84.4)	0.426
Terlipressin 6 hourly over 24 h	15 (24.2)	14 (43.8)	0.052
Requirement for blood transfusion (mean number of units)	2 ± 1 units	2 ± 1 units	-

[1]Significant risk factor. PPF: Periportal fibrosis; MELD: Model for end stage liver disease.

Table 3 Endoscopy findings and endoscopic management in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)

Variable	PPF (*n* = 62)	Cirrhosis (*n* = 32)	*P* value
Grade Ⅱ OV	5 (8.1)	2 (6.3)	0.961
Grade Ⅲ OV	17 (27.4)	10 (31.3)	
Grade Ⅳ OV	23 (37.1)	14 (43.8)	
Gastric varices	17 (27.4)	6 (18.8)	
Band ligation	8 (12.9)	1 (3.1)	0.318
Sclerotherapy	45 (72.6)	28 (87.5)	
Histoacryl injection	4 (6.5)	2 (6.3)	
Both histoacrylandscleroth erapy/band	5 (8.1)	1 (3.1)	

OV: Oesophageal varices; PPF: Periportal fibrosis.

a significant risk factor for 6-wk mortality (*P* value < 0.018) (Table 5).

In group B, rebleeding within the 6-wk follow-up period and blood transfusion on admission were significant risk factors for mortality (*P* value < 0.005 and < 0.049 respectively) (Table 6).

Rebleeding rate

The 6-wk and 5-d rebleeding rate in group A were 56% and 25% respectively compared to 32% and 3% in group B (*P* value < 0.015 and < 0.002) (Table 4).

Factors related to variceal rebleeding within 6 wk

In group A, no significant factors were related to rebleeding within 6 wk.

In group B, grade Ⅲ PPF and blood transfusion on admission were significant risk factors associated with rebleeding in this group with a *P* value < 0.004 and < 0.02 respectively (Tables 5 and 6).

Factors related to variceal rebleeding within 5 d

In group A, clinical presentation with encephalopathy was a significant risk factor for rebleeding within 5 d (*P* value < 0.005). In group B there were no significant factors

Table 4 Study outcomes in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)

	PPF (*n* = 62)	Cirrhosis (*n* = 32)	*P* value
Mortality at 6 wk	10	53	0.000[1]
Mortality at 5 d	0	16	0.004[1]
Rebleeding at 6 wk	32	56	0.015[1]
Rebleeding at 5 d	3	25	0.002[1]

[1]Significant risk factor. PPF: Periportal fibrosis.

contributing to rebleeding within 5 d (Tables 5 and 6).

DISCUSSION

In this study, we evaluated early mortality and rebleeding following AVH. In this part of Africa minimal data is available with regards to mortality following AVH due to scarcity of endoscopy services. This study is unique because we evaluated the patients in two groups according to the etiology of the underlying liver disease, either liver cirrhosis or schistosomal periportal fibrosis. Previous studies on early mortality following AVH were done exclusively on patients with liver cirrhosis[3,11-13].

In this study, in the cirrhosis group, the 6-wk and 5-d mortality were both high at 53% and 16% respectively, whereas the 6-wk mortality following AVH in patients with schistosomal PPF was 10% with no deaths reported during the first 5 day (*P* value < 0.000 and < 0.004). This high rate of mortality in cirrhosis following variceal bleeding is well described by D'Amico; where four clinical stages of cirrhosis were agreed upon in the Baveno Ⅳ consensus conference. Each stage with different features and a different prognosis as follows: Stage 1 no varices or ascites, mortality rate is 1%, stage 2 varices without ascites and without bleeding, mortality rate is 3.4% per year, stage 3 is characterised by ascites with or without varices but never bled, mortality rate is 20% per year, stage 4 is characterised by GI bleeding with or without ascites, in this stage the one year mortality is 57% and

Table 5 Factors associated with mortality and rebleeding in 32 patients with liver cirrhosis

Study outcome	Factors	*P* value
Mortality at 6 wk	CTP score C	0.018[1]
Mortality at 5 d	CTP score C	0.029[1]
	Rebleeding within 5 d	0.049[1]
Rebleeding at 6 wk	Non	Non
Rebleeding at 5 d	Encephalopathy	0.005[1]

[1]Significant risk factor. CTP: Child-Turcotte-Pugh.

Table 6 Factors associated with mortality and rebleeding in 62 patients with periportal fibrosis

Study outcome	Factors	*P* value
Mortality at 6 wk	Blood transfusion	0.049[1]
	Rebleeding within 6 wk	0.005[1]
Mortality at 5 d	Non	Non
Rebleeding at 6 wk	Blood transfusion	0.021[1]
	Grade Ⅲ PPF	0.004[1]
Rebleeding at 5 d	Non	Non

[1]Significant risk factor. PPF: Periportal fibrosis.

nearly half of these deaths occur within 6 wk from the initial episode of bleeding[14].

This difference in mortality rate between the two groups is most likely due to preserved liver cell function in most patients with PPF compared to patients with liver cirrhosis[15]. In this study we observed that only a minority of patients with schistosomal PPF presented with clinical evidence of liver cell failure; mainly ascites in 2% and encephalopathy in 3%, it has been reported that a few patients with schistosomiasis do evolve to an end stage of the disease with hepatocellular failure, this is known as decompensated schistosomiasis[15].

Le Moine *et al*[3] reported predictive factors for mortality at 6 wk in cirrhotic patients being prolonged prothrombin time, encephalopathy and number of blood units transfused. Krige *et al*[12] found in a study done exclusively in alcoholic cirrhosis, that CTP class C, encephalopathy, ascites, bilirubin > 51 mmol/L, INR > 2.3, albumin < 25 g/L and patients who require balloon tamponade were factors related to 6-wk mortality. In this study we also found that the CTP class C was significantly related to 6-wk mortality (*P* value < 0.02) this was similar to findings in other studies[3,12,13]. Furthermore factors related to mortality within the first 5 d following AVH in cirrhosis were again the CTP class C and the rebleeding within these 5 d. Bambha *et al*[11] suggested that the MELD score rather than CTP class was more powerful in predicting 6-wk mortality. In this study, the MELD score was not a significant risk factor for mortality. We found that mortality following AVH in schistosomal PPF (10%) is much less when compared to cirrhotic patients (56%). There is scanty data on the early outcomes of patients with schistosomal PPF presenting with AVH, however, a study from Tanzania found that mortality following AVH in patients with schistosomal PPF after 8 wk of follow-up was quite similar to this study at 10%[16]. In this study, no deaths occurred within the first 5 d in the PPF group.

Factors significantly contributing to the 6-wk mortality in PPF included blood transfusion within the first 24 h and rebleeding within the 6-wk follow-up period (*P* values < 0.049, < 0.005 respectively). The 6-wk rebleeding rate in the PPF group was (32%), less than cirrhosis group at 56% (*P* value < 0.004). Significant factors contributing to the 6-wk rebleeding rate in PPF group were grade Ⅲ PPF on abdominal ultrasound and blood transfusion on admission (*P* value < 0.004 and < 0.02 respectively). A previous study from Sudan demonstrated that rebleeding was more in grade Ⅲ PPF[17]. A study from Brazil also found that the sonographic grade of periportal fibrosis was an important tool in predicting variceal complications in patients with schistosomal PPF[18], whereas the longitudinal spleen dimension of more than 11 cm, was an important tool in predicting variceal bleeding in another study[6]. It is well known that a conservative blood transfusion strategy is associated with better survival outcomes in patients with upper gastrointestinal bleeding[19]. In this study blood transfusion was provided to 58% of patients with PPF with a mean of 2 ± 1 units of blood. Requirement of blood transfusion was a significant factor for both mortality and rebleeding in PPF group (*P* value < 0.049 and < 0.02 respectively).

Rebleeding within 5 d in PPF occurred in two patients (3%), which is much less than in cirrhosis group at 25% (*P* value < 0.002). Both patients had grade Ⅲ PPF, were hemodynamically stable and did not require blood transfusion, however, none of the factors evaluated contributed to rebleeding within 5 d. Further studies are needed to reveal other causes contributing to rebleeding such as the portal vein pressure and intra variceal pressure.

In this study, the rebleeding rate among cirrhosis group was high at 56% and 25% of these patients developed rebleeding within the first 5 d. The 6-wk rebleeding rate reported in literature was 16.2%, 30% and 24.2%[2,12,13].

It has been reported that the severity of liver disease in terms of presence of ascites and encephalopathy contributes to the rebleeding rate[3,12]. In this study, the presence of hepatic encephalopathy in patients with cirrhosis was a significant factor for rebleeding within 5 d of AVH (*P* value < 0.005). Non of the other factors evaluated were found significant for 6-wk rebleeding in cirrhosis, perhaps larger studies with bigger sample sizes are needed to reveal the factors contributing to rebleeding in patients with cirrhosis in our region.

It is known that the use of vasopressor agents improve outcomes following AVH[20]. In this study, Terlipressin was provided to patients whenever available, however there was no significant difference on survival or rebleeding rate between patients with liver cirrhosis and patients PPF with use of Terlipressin.

In patients with PPF and cirrhosis the mean portal vein diameter was 17.4 ± 3.3 mm and 16.4 ± 3.1 mm

respectively, reflecting high portal pressure and hence high variceal pressure. Therefore, effective lowering of portal pressure should be paramount in order to prevent the dreadful complication of variceal bleeding.

HBsAg seroprevelance among PPF patients was 6%, similar to seroprevelance of HBsAg among the general population in central Sudan[21], hence HBV screening and vaccination in patients with PPF should be encouraged.

In conclusion, this study has demonstrated that the 6-wk and 5-d mortality and rebleeding are significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis. Effective secondary prophylaxis after AVH needs to be adhered to and when resuscitating patients with AVH, blood transfusion should be given carefully and HBV vaccination should be actively encouraged.

COMMENTS

Background

Variceal bleeding is a devastating complication of portal hypertension. In patients with liver cirrhosis the risk of rebleeding after acute variceal haemorrhage is highest within the first 6 wk with a peak in the first 5 day.

Research frontiers

In Sudan, a country endemic with schistosomiasis, acute variceal haemorrhage (AVH) in the majority of cases is caused by portal hypertension due to schistosomal periportal fibrosis, while cirrhosis is less common. The 6-wk and 5-d mortality and rebleeding following AVH in schistosomal portal hypertension have not been well studied.

Innovations and breakthroughs

In this study, the authors evaluated early mortality and rebleeding following AVH. In this part of Africa minimal data is available with regards to mortality following AVH due to scarcity of endoscopy services. This study is unique because the authors evaluated the patients in two groups according to the etiology of the underlying liver disease, either liver cirrhosis or schistosomal periportal fibrosis. Previous studies on early mortality following AVH were done exclusively on patients with liver cirrhosis.

Applications

This study has demonstrated that the 6-wk and 5-d mortality and rebleeding are significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

Terminology

Schistosomiasis is endemic in Sudan; the mortality of schistosoma mansoni infection is mostly due to development of periportal fibrosis with subsequent development of portal hypertension and oesophageal varices causing significant morbidity and mortality.

Peer-review

This is a well conducted prospective study about variceal bleeding complications in African Setting.

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