Original article:

Infections and coagulopathy as predictors of varietal bleeding in patients with portal hypertension: A case-control study

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Abstract:

Background: Upper gastrointestinal endoscopy is the gold standard test for the diagnosis of variceal hemorrhage; however it is relatively invasive and may not be available in rural outreaching areas. Hence non-invasive available tests are needed.

Objective: The current study aimed at assessing infections, prothrombin time and platelets counts as predictors of bleeding esophageal varices in patients with portal hypertension due to Peri portal fibrosis.

Subjects and Methods: This is a case control study, conducted among 100 patients with bleeding esophageal varices and 100 controls with non-bleeding esophageal varies. The survey was carried out in Ibn Sinna teaching hospital (Tertiary hospital of gastroenterology with a special center for upper GI bleeding), Khartoum, Sudan, during the period of April to September 2013. The participants were screened for urinary tract infection, upper respiratory tract infection and malaria. Full blood count, prothrombin time and high C-reactive protein were also measured.

Results: Among 100 patients with bleeding varices and 100 controls, males were 86% in the study group and 78% among controls. Fever, leukocytosis, neutrophilia, diarrhea and ascites were predictors of variceal hemorrhage with a P value of < 0.05, while productive cough, urinary symptoms, platelets count and serum albumin, and highly sensitive C-reactive protein were not significant.

Conclusions: Prothrombin time and leukocytosis may predict bleeding esophageal varices. Similar further larger multi-center studies are recommended.

Key words: Predictors, bleeding esophageal varices, Sudan.

Introduction:

Acute variceal hemorrhage is a serious cause of mortality in the emergency departments and can be difficult to treat. In general, upper gastrointestinal (GI) hemorrhage accounts for around 102 hospitalizations per 100,000 people every year, and esophageal varices represent approximately 14% of these cases. Furthermore, esophageal varices are the most common cause of persistent and severe upper GI hemorrhage, accounting for approximately 33% of these events. Among patients with cirrhosis, 70% of

upper GI bleeding episodes are caused by esophageal varices. Gastroesophageal varices exist in nearly 50% of patients with cirrhosis at the time of initial diagnosis(1) . Among those who survive, subsequent rebleeding occurs in another one third within 6 weeks of the index bleeding and more than 80% of the rebleeding episodes occur within 2 weeks (2). Oesophageal variceal rupture is the commonest cause of upper gastrointestinal bleeding in central Sudan. In 90% of patients it is secondary to Schistosomal portal hypertension. The majority of these patients are young and their disease is characterized by a benign course compared to cirrhosis. However, a major cause of death in these patients is acute variceal bleeding (3). Studies showed that bacterial infection is one of the factors influencing variceal bleeding .In one of these Studies there is higher incidence of bacterial infection among patients with acute bleeding with portal hypertension (25 of 35 patients, 71%) compared to patients with liver cirrhosis and portal hypertension without acute bleeding (14 of 35 patients, 40%, $p < 0.01$) (4). Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients, developing in up to 66% (20% within the first 48 hours, 35–66% occurs within two weeks (5). About two thirds of these infections are present at hospital admission while the remainder develops during admission. Moreover, bacterial infections are more common in cirrhotic patients with acute variceal bleeding than in those admitted to hospital with other forms of decompensation, such as encephalopathy. Recently, bacterial infections and/or endotoxaemia have been associated with failure to control variceal bleeding, more early variceal rebleeding, abnormalities in coagulation , vasodilatation of the systemic vasculature, and worsening liver function (6 & 7). There are many potential mechanisms by which bacterial infections can influence variceal bleeding. Endotoxins can increase portal pressure and so participate in development of bleeding which may play a pivotal role in activating clotting system in portal and systemic circulation and impair liver function (8). Most of these studies were done in patients of portal hypertension due liver cirrhosis in contrast to our study, which was carried among patients with portal hypertension due to periportal fibrosis to assess whether infections and coagulopathy influence variceal bleeding group. Urinary and respiratory tract infections, malaria, platelets count and prothrombin time among patients with schistosomal portal hypertension in Sudan were assessed.

Subjects and Methods:

This is a case-control study, conducted among 100 patients with portal hypertension due to periportal fibrosis, who presented to the bleeding center at Ibn Sina Specialized Hospital with upper GIT bleeding (Group A) and patients with portal hypertension due to periportal fibrosis, who came for routine follow up to the Portal Hypertension (PHT) Specialized referred clinic. The study was conducted during the period of April to September, 2013. Patients with bleeding esophageal varices due to causes other than periportal fibrosis were excluded. A structured questionnaire was used to collect; Age, sex, residence, occupation, fever, urinary symptoms, cough, diarrhea, jaundice, ascites, acute malaria, the total white blood count, hemoglobin, and platelets from the patients records. The prothrombin time, urinary sediments and C - reactive protein were measured.

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For the purpose of the survey; fever, urinary symptoms, cough, diarrhea, acute malaria, urinary sediments and C - reactive protein were considered as markers for infections, while low platelets counts and prolonged prothrombin time as bleeding and coagulopathy markers.

All the participants signed a written informed consent, and the ethical committee of the Sudan Council Specialization Board has approved the research proposal. Ethical clearance was obtained from Sudan Medical Specialization Board. The Statistical Package for Social Sciences (IBM, version 16, New York was used for data analysis). A p-value of <0.05 was considered significant.

Conflict of interest: Authors declares no conflict of interest in this article.

Results: Out of 100 patients with esophageal varices and 100 control subjects (86% were males vs. 78% among controls), 39% of patients were farmers vs. 40% of controls. Professionals were 12% and 11% respectively, other participants characters were depicted in (Table 1).

In the current survey, fever was positive in 31% of patients and 16% of controls with significant statistical difference, P-value 0.012, urinary symptoms were present in 17% vs. 18% with no significant statistical difference, P-value 0.850, productive cough was reported in 11% of patients and 10% of controls, P-value 0.818, significant statistical differences were detected in diarrhea and ascites (9% vs. 1%, and 17% vs. 6%, P-values 0.009 and 0.015 respectively (Table 2).

This study showed no significant differences between subjects and controls regarding malaria, and platelets count (6% among subjects and 4 among controls for malaria, P-value (> 0.5, and 62% vs. 72%, P-value 0.113). High significant statistical differences were present regarding leucocyte counts (10% vs. 1%), and prothrombin time (71% vs. 24%), P-value (< 0.001) (Table. 3).

In the present study high pus cells in the urine were present in 25% of subjects and 18% of the controls, while high RBCs were found in 16% of patients and 27% of control subjects Figure (1)

Discussion:

This study was conducted in the Mohammed Salih Idris GI bleeding center and Ibn –Sina Specialized Hospital (Portal Hypertension Clinic) Khartoum Sudan, in the period between April 2013 and September 2013, with the aim of studying the correlation- if any- between variceal bleeding among periportal fibrosis portal hypertension patients. Most of the patients are of less than 50 years age (65.5%) this is similar to a study in Sudan (9), reflecting the heavy economic impact of the disease where it affects the reproductive age group. Males represent the majority of the study population (79%) coinciding with the local data (10).

Incidence of infections among esophageal variceal bleeding patients in this study was significant among group (Group A) compared to the control group (Group B) as evidenced clinically by the presences of fever (31% in bleeders vs. 16% for the control with a P value of (0.012), the leukocytosis and neutrophilia (10% vs 1% and 13% vs 1% respectively P. value is (0.000). This result is compatible with a study done by Husová L and et al (11), indicating a statistically higher incidence of bacterial infection among patients with acute bleeding and portal hypertension (25 out of 35 patients, 71%) compared to patients with liver cirrhosis and portal hypertension, without acute bleeding (14 out of 35 patients, 40%. The P. value is (< 0.01), this is also similar to what was found in other studies (12, 13 & 14).

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It is hypothesized that the release of endotoxin into the systemic circulation during bacterial infections could increase the portal pressure through the induction of endothelin and vasoconstrictive cyclooxygenase products. Furthermore, endotoxin-induced nitric oxide and endothelin-induced prostacyclin could inhibit platelet aggregation, which may result in a further deterioration of primary hemostasis at the level of the esophageal varices (15).

This study showed, statistically significant increase in the incidence of coagulopathy (INR more than 1.2) in bleeders (Group A) than in non-bleeders (Group B) ,(48% vs. 24% P. value (0.000) ,similar to a study done in patients with hepatosplenic schistosoma Mansoni and Advanced periportal fibrosis by Luiz Arthur Calheiros Leite et al, in Brazil (16), in which, they reported a significant (40%) increase in the INR and reduced levels of factor VII and protein C in patients, compared to the controls. It is also similar to a study done in Egypt showing prolongation of the PT and PTT in bilharzial patients compared to controls (17).

In this study there is statistically significant increase in the incidence of ascites in bleeders (Group A) compared to the non-bleeders (Group B), (17% vs. 6% P. value 0.000) this can be explained by the transient hepatic decompensation in patients with massive bleeding.

Conclusion: Leukocytosis, neutrophilia, diarrhea, ascites, and prolonged prothrombin time may predict bleeding esophageal varices. Further multi-center studies concentrating on specific infections are recommended.

Table1: General characters of the study group

Character	**Cases**	**Control**
Sex		
Males	86 %	73 %
Females	14 %	27 %
Occupation		
Farmers	39 %	40 %
Professionals	12 %	11%
Not working	13 %	27 %
laborer	32 %	11 %
Residence		
Gezira (central Sudan)	60 %	56 %
Khartoum	13 %	15 %
Sinnar	4 %	8 %
White Nile	16 %	17 %
Western Sudan	1 %	4 %
Eastern Sudan	6 %	2 %
Jaundice	6 %	4 %

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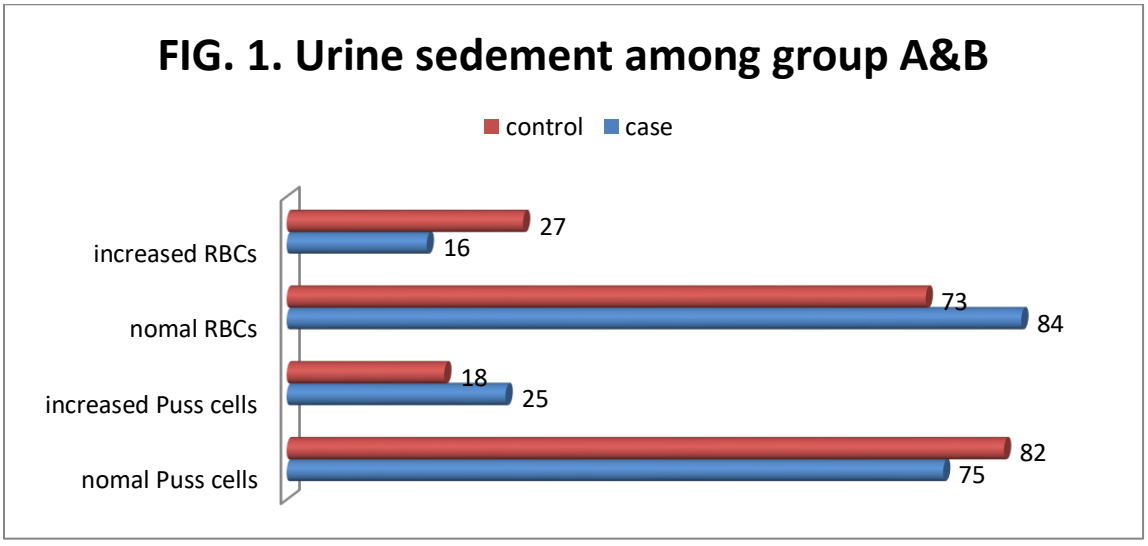
Table 2: History and examination results of the study group

Character	Cases	Control	P-value
Fever	31 %	16 %	0.012
Urinary symptoms	17 %	18 %	0.850
Productive cough	11 %	10 %	0.818
Diarrhea	9 %	01 %	0.009
Ascites	17 %	06%	0.015

Table 3: Investigations results of the study group

Character %	Cases	Control	P-value
Blood film for malaria	06 %	04 %	0.50
Leukocytosis	10 %	01 %	<0.001
Neutrophilia	13 %	01 %	<0.001
Low platelets count	62 %	72 %	0.113
Prolonged prothrombin time	71 %	24 %	<0.001
Low albumin (<3.5g/dl)	29 %	21 %	0.191
High C-reactive protein	24 %	17 %	0.338



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