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Predictors of Bleeding from Esophageal Varices: The Role of Factor VII and von Willebrand Factor (vWF)

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Abstract

***Objectives*: Bleeding from gastroesophageal varices is the most serious and life-threatening complication of cirrhosis and accounts for 10% of all cases of bleeding from the upper GI tract. It is essential to identify and treat those patients at the highest risk because each episode of variceal hemorrhage carries a 20 percent to 30 percent risk of death, and up to 70 percent of patients who do not receive treatment die within one year of the initial bleeding episode. The aim of this study is to determine the clinical predictors of bleeding esophageal varices and study the role of F VII (factor VII) and vWF (von willebrand factor) in predicting bleeding in patients with eosphogeal varices. *Methods*: A case control study was done on all patients with esophageal varices admitted at Sohag and Qena faculty of medicine hospitals from January 2012 to August 2013. Various clinical, laboratory and endoscopic variables were tested to determine the predictors of esophageal bleeding. *Results*: Among 300 patients with esophageal varices, 80 percent was due to hepatitis C virus (HCV), 18 percent was due to hepatitis B virus (HBV), and 2 percent had both HCV and HBV. As an etiologic factor for their liver disease, hemoglobin was 10.12 ± 2.26 g/l, platelet count 135.55 ± 65.94 × $l0^9$/l, prothrombin time 14.1 ± 0.92 second, albumin 2.88 ± 0.71 g/dl, ALT 48.25 ± 24.15 u/l, total bilirubin 1.92 ± 1.36 mg/dl. Factor VII was 27.4 ± 8.92 percent and vWF was 188.33 ± 13.66 IU/dl. Splenomegaly was reported 79.6 percent, 90.3 percent had ascites. 35 percent had grade III esophageal varices, 29 percent had four-column esophageal varices on endoscopy, 13.7 percent had concomitant gastric varices and 38.3 percent had portal hypertensive gastropathy. Platelet count, presence of red color sign, the number of columns of esophageal varices, presence of portal gastropathy on eosphagogastroduodenoscopy (EGD) showed a significant positive correlation with bleeding. There is a significant decrease of FVII and a significant increase of vWF in**

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bleeding group in comparison with non bleeding group. *Conclusion*: Thrombocytopenia, presence of encephalopathy and endoscopic findings of large varices, presence of red color sign, and portal hypertensive gastropathy were found to be predictors of esophageal variceal bleeding. Increase of vWF and decrease of FVII are laboratory predictors of esophageal variceal bleeding.

Keywords

Esophageal Varices; FVII; von Willebrand Factor

1. Introduction

Bleeding from gastro-oesophageal varices is the most serious and life-threatening complication of cirrhosis and accounts for 10% of all cases of bleeding from the upper GI (gastrointestinal) tract. Despite the advances in treatment of variceal bleeding, mortality remains high at around 40%, being closely related to the severity of underlying liver disease as assessed by child's class and impairment of renal function [1].

Clinical factors associated with an increased risk of a first variceal hemorrhage include continued alcohol use and poor liver function. Endoscopic predictors of bleeding include endoscopic red signs on the variceal wall and large varices [2].

Thrombocytopenia, ascites and splenomegaly are useful non invasive parameters to predict bleeding from esophageal varices [3]. Factor (F)V and factor VII (FVII) levels are sensitive indicators of hepatic protein synthesis often used to assess the severity of disease [4] [5]. FVII is the first clotting factor level to fall, because of its short half-life of 6 hours. FVII deficiency develops in 75% - 85% of patients, and levels range from 23% to 74% of normal in compensated cirrhosis [4]-[7]. FVII levels are significantly lower in decompensated cirrhosis, but 30% of normal ones are in most patients with stable disease [4] [5] [8].

The elevated levels of vWF (von Willebrand factor) in cirrhosis may be a consequence of endothelial perturbation, possibly caused by bacterial infection [5]. Another possible mechanism of elevated vWF in cirrhosis is induction of synthesis of vWF in the liver with cirrhosis itself [8] or reduced liver-mediated clearance. Although it is established that vWF antigen levels are increased in patients with cirrhosis, relatively little is known on the relation between it and the bleeding from esophageal varices [9] [10] so we aimed in this study to determine the clinical predictors of bleeding esophageal varices and study the role of FVII and vWF in predicting bleeding in patients with eosphogeal varices.

2. Materials and Methods

All patients with a clinical diagnosis of liver cirrhosis who underwent endoscopy at Qena and Sohag faculty of medicine hospitals from January 2012 to August 2013 were divided into 2 groups. Group A consisted of patients with a history and clinical presentation of bleeding esophageal varices and Group B were those patients with esophageal varices on endoscopy but with no history of variceal bleeding. The diagnosis of cirrhosis was based on a combination of clinical, laboratory and radiographic criteria.

Bleeding esophageal varices is defined as those patients who presented with upper gastrointestinal bleeding manifested by hematemesis, melena and/or hematochezia with endoscopic confirmation of esophageal variceal bleeding and no other bleeding lesion seen on endoscopy. Patients with a clinical diagnosis of upper gastrointestinal bleeding due to acquired coagulopathy, gastric ulcers, duodenal ulcers or gastric varices were excluded. All patients underwent complete clinical examination, abdominal sonography laboratory investigations and upper GIT endoscopy.

Forty patients from each group A and B are randomly selected and Factor VII and vWF are estimated.

2.1. Abdominal Ultrasound Findings

- portal vein diameter
- splenomegaly
- ascites

2.2. Endoscopic Data

Esophageal varices were graded according to Japanese Research for Portal Hypertension Classification System as follows: grade (Gr) I: small esophageal varices which flatten with insufflation or minimally protrude into the esophageal lumen, Gr II: moderated sized varices with minimal obscuring of the gastroesophageal junction, Gr III: large varices showing luminal proplapse substantially obscuring the gastroesophageal junction and Gr IV: very large esophageal varices completely obscuring the gastroesophageal junction and do not flattens on insufflation. The number of variceal columns, presence of red color sign, presence of gastric varices and portal gastropathy were also recorded.

2.3. Laboratory Investigations

7 ml venous blood was obtained from all patients and divided in 3 tubes, one on EDTA for CBC, the second on Na citrate for prothrombin time and coagulation factors and the third contain no anticoagulant for the biochemical tests. The laboratory investigations were included CBC, AST, ALT, prothrombin time and concentration, albumin and bilirubin level, factor VII and vWF.

2.4. Factor VII Assay Principle

Factor VII was measured using the Sysmex CA-1500 System, a fully-automated blood coagulation analyzer. Coagulation factor VII deficient plasma is a human plasma-based reagent for the detection of hereditary or acquired deficiencies of factor VII. It is manufactured by immunoabsorption and contains a residual factor concentration of <1% factor VII and normal levels of fibrinogen and other extrinsic clotting factors.

2.5. vWF Assay Principle

vWF is measured by VIDAS automated immunoassay system. A new automated quantitative enzyme linked immunosorbent assay (ELISA) for the detection of human von Willebrand factor, VIDAS vWF, has been developed for use on the VIDAS analyzer (BioMérieux). The two-step capture/tag test relies on two monoclonal antibodies [mAbs], the second one being labelled with alkaline phosphatase.

3. Statistical Analysis

Data were analyzed utilizing the STATA SOFTWARE. Continuous variables were expressed as means ± standard deviation and nominal variables were recorded as frequencies. Student's unpaired *t* test or Mann–Whitney test were used to compare continuous variables. The Chi2 test was used to identify differences between categorical variables. *P* values less than 0.05 was considered to indicate statistical significance.

4. Results

From January 2012 to August 2013, three hundred liver cirrhotic patients underwent endoscopy. One hundred and sixty patients with esophageal variceal hemorrhage made up the study group and one hundred and forty patients with esophageal varices but no history of variceal hemorrhage comprised the negative control group. Two hundred and Forty (80%) had Hepatitis C, Fifty Six (18%) had hepatitis B, Six patients 2% had both hepatitis B and C, 2% of all patients had HCC per biopsy factors for their liver disease. Male compromised 86% of the study population with a mean age of 42 years. The Physical examination are listed in **Table 1**, laboratory findings are listed in **Table 2**, there is significant decrease of hemoglobin level and platelet count in bleeding group when compared with non bleeding group. Also **Table 2** shows significant increase in von Willebrand factor and significant decrease in FVII in bleeding group when compared with non bleeding group

No significant difference between both groups as regard splenomegaly, presence of ascites and presence of splenic or hepatic collaterals as shown in **Table 3**.

Endoscopic findings are listed in **Table 4**. High grade of varices, presence of red color sign [RC], number of columns of EV, presence of gastric varices and presence of portal gastropathy were significantly correlated with increased risk of bleeding from esophageal varices. RC sign is the most sensitive and specific sign for bleeding as shown in **Table 5**.

Table 5 shows the sensitivity, specificity and accuracy of various predictors of bleeding including the

Table 1. Signs of clinical examination.

Parameter	Bleeding group No. [Percent]	Non bleeding group No. [Percent]	P value	All patients No. [Percent]
Encephalopathy:				
Grade 0	71 [44.4%]	116 [82.9%]	0.001	187 [62.3%]
Grade1	58 [36.2%]	20 [14.3%]		78 [26%]
Grade 2	21 [13.1%]	4 [2.9%]		25 [8.3%]
Grade 3	6 [3.8%]	0 [0%]		6 [2%]
Grade 4	4 [2.5%]	0 [0%]		4 [1.3%]

Table 2. Laboratory data.

Parameter	Bleeding group [Mean + SD]	Non bleeding group [Mean + SD]	P value	All patients [Mean + SD]
ALT	48.10 ± 17.28	48.43 ± 30.37	NS	48.25 ± 24.15
Proth time.	14.2 ± 0.84	14.0 ± 0.79	NS	14.1 ± 0.92
Total bilirubin	2.01 ± 1.41	1.87 ± 1.26	NS	1.92 ± 1.36
Albumin	2.83 ± 0.57	2.93 ± 0.61	NS	2.88 ± 0.71
Haemoglobin	8.74 ± 1.82	11.68 ± 1.59	0.001	10.12 ± 2.26
Platelet count	105.06 ± 49.33	170.41 ± 65.39	0.001	135.55 ± 65.94
Factor VII	21.2 ± 8.12	34.4 ± 6.08	0.001	27.4 ± 8.92
vWF	196.34 ± 12.6	179.17 ± 11.2	0.001	188.33 ± 13.66

NS: non significant.

Table 3. Sonographic findings.

Parameter	Bleeding group No. [Percent]	Non bleeding group No. [Percent]	P value	All patients No. [Percent]
Splenomegaly:	129 [80.6%]	110 [78.5%]	NS	239 [79.6%]
PVD:	85 [53.1%]	68 [48.6%]	NS	153 [51%]
Degree of ascites:				
Minimal	39 [24.4%]	37 [26.4%]	NS	76 [25.3%]
Mild	41 [25.6%]	32 [22.9%]		73 [24.3%]
Moderate	48 [30%]	42 [30]		90 [30%]
Marked	17 [10.6%]	15 [11.4%]		32 [10.6%]
Collatralls:	48 [30%]	41 [29.2%]	NS	89 [29.7%]

NS: non significant.

sensitivity and specificity of low FVII (<28.2%) and high vWF (>187.1 IU/dl) to predict bleeding in patients having esophageal varices. The sensitivity of FVII and vWF were 75% and 82.5% respectively while the specificity were 85% and 65% respectively. We found no significant difference between patients with HCV infection and patients with HBV infections as regard the previous predictors of bleeding.

5. Discussion

Variceal hemorrhage is a major source of mortality of patients with portal hypertension [11], gastroesophageal varices are present in 50% - 60% of cirrhotic patients. The natural history of liver cirrhosis shows that 30% of patients with liver cirrhosis will experience an episode of variceal hemorrhage within one year of diagnosis of varices [12]. Endoscopy proved to be a powerful tool for the determination of bleeding risks. Higher grade esophageal varices, red color sign, portal gastropathy and presence of fundal varices are other predictors of bleeding in esophageal varices. Our study has shown that large varices are more likely to bleed than small ones. Bleeding

Table 4. Endoscopic finding.

Parameter	Bleeding group No. [Percent]	Non bleeding group No. [Percent]	P value	All patients No. [Percent]
Grade of varices:				
Grade 1	7 [4.4%]	112 [80%]	0.01	119 [39.7%]
Grade 2	29 [18.1%]	18 [12.8%]		47 [15.7%]
Grade 3	98 [61.3%]	7 [5%]		105 [35%]
Grade 4	29 [18.1%]	0 [0%]		29 [9.7%]
Number pf varices:				
One varix	9 [5.6%]	62 [44.3%]	0.001	71 [23.7%]
Two varices	10 [6.3%]	69 [49.3%]		79 [26.3%]
Three varices	56 [35%]	8 [5.7%]		64 [21.3%]
Four varices	85 [53.1%]	1 [0.7%]		86 [28.7%]
Red sign:	144 [90%]	9 [6.4%]	0.001	153 [51%]
Gastric varices:	28 [17.5%]	13 [9.3%]	0.039	41 [13.7%]
Portal gastro:	103 [64.4%]	12 [8.6%]	0.001	115 [38.3%]

Table 5. Statistical parameters of various predictors of bleeding.

Parameter	Accuracy%	Sensitivity%	Specificity%
Low platelet count [<137 94 × $l0^9$/l]	75.5	65.7	84.4
Encephalopathy	68.3	82.9	55.6
≥ 3 varices	88.3	80	95.6
Red color sign	91.7	93.6	90
Portal gastropathy association	77	91.4	64.4
High vWF [>187.1 IU/dl]	73.8	82.5	65
Low FVII [<28.2%]	80	75	85

was present in 61.3% of our patients with grade 3 and in 18.1% with grade 4 varices. Wall tension is a factor of diameter and wall thickness, and it is not surprising that larger varices are more likely to rupture. Variceal size has been investigated by many researchers [13] [14]. All of them have documented the fact that larger varices bleed more often than smaller varices. The only exception to this is only one study found that 35% of patients with small varices bled, while only 20% of patients with large varices also bled [15].

Another endoscopic finding of value in predicting variceal bleeding is the appearance of the vessel wall. The color of varices is thought to predict impending hemorrhage. Our study has shown that endoscopic finding of "red signs" is related to the variceal bleeding. The "red signs" were found in 90% of varices with bleeding. The red color signs are the result of microteleangioectasia of the varix. This agrees with many previous studies [16] [17]. In addition, the presence of concomitant gastric varices could be added as a further criterion for the prediction of bleeding from esophageal varices.

In agreement with previous, the presence of gastric varices in predicting bleeding from esophageal varices is noteworthy. Close anatomical connections have been demonstrated between the veins of the stomach and the distal esophagus. Furthermore, the presence of the varices in the gastric fundus indicates a particularly high venous blood pressure in that area thus offering an explanation for the increased bleeding risk [16]-[18].

In our study we found another criterion in predicting bleeding from esophageal varices is the presence of portal gastropathy on endoscopy. Prevalence of hypertensive gastropathy parallels the severity of portal hypertension and liver dysfunction. A high portal pressure [>12 mmHg] can explain the snake skin appearance of gastric mucosa on endoscopy and positively correlates with the risk of bleeding this agree with ***previous studies*** [16]. We also found that increase the number of varices predicting bleeding from esophageal varices.

In patients with liver cirrhosis elevated levels of von Willebrand factor antigen are found frequently but the clinical significance is unclear. VWF-Ag plays an important role in primary haemostasis and development of thrombotic vascular obliteration is discussed as a possible mechanism leading to portal hypertension [19]. Endothelial dysfunction is a major determinant of the increased hepatic vascular tone of cirrhotic livers. Von Willebrand factor [vWF], surrogate markers of endothelial dysfunction, is increased in patients with cirrhosis. So the vWF is increased in bleeding patients as increase of portal hypertension [20].

In our study we found that the increase of vWF correlates with the increased risk of bleeding form oesophageal varices as it significantly higher in patient with bleeding so it is significant predictor of bleeding.

Factor [F]V and FVII levels are sensitive indicators of hepatic protein synthesis often used to assess the severity of disease [4] [5]. FVII is the first clotting factor level to fall, because of its short half-life of 6 hours. FVII deficiency develops in 75% - 85% of patients, and levels range from 23% to 74% of normal in compensated cirrhosis [4] [6] [7]. FVII levels are significantly lower in decompensated cirrhosiss.

In our study significant decrease in FVII in bleeding group. Clinical trials are needed to better define the role of recombinant activated factor VII in the treatment of bleeding complications of liver disorder [21].

6. Conclusion

Our study concludes that vWF and FVII could be used as predictors for bleeding in patients having esophageal varices but further additional work should be done to study their roles in management.

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