Study of the causes associated with variceal rebleeding in hepatic cirrhosis

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Abstract: *Background:* Esophageal variceal (EV) bleeding is a frequent and severe complication in patients with cirrhosis. Cirrhotic patients with acute EV bleeding are characterized by a high mortality and considerable rebleeding rate. Although therapeutic approaches such as pharmacological treatment and band ligation or transjugular intrahepatic portosystemic shunt (TIPS) have been developed to prevent rebleeding, mortality in these patients remains as high as 30%–50% . Aims: Is to explore factors associated with variceal rebleeding in cirrhotic patient. *Methods:* This study was conducted on 200 cirrhotic patients who were admitted to Tanta University Hospital between April 2012 and October 2012 because of variceal bleeding. These patients were divided into 2 groups: *Group I:* Cirrhotic patients presented with rebleeding after previous endoscopic treatment of known varices within 6 weeks of acute bleeding. *Group II:* Cirrhotic patients who admitted with variceal bleeding and didn't develop early or late rebleeding in regular follow up session. all patients were subjected to history taking, liver and renal function tests, CBC , urine and ascitic fluid analysis, chest X-ray and abdominopelvic US. *Results:* analysis of the clinical results of the present work revealed that rebleeding was significantly higher with advanced liver disease as 67% (Child C), 11% Child A in group I, the volume of ascites as in group I (72%) with moderate and massive ascites versus (28%) with mild and no ascites, presence of infection included chest infection by 38% in group I, 11% in group II.S.B.P by 15% in group I, 6% in group II. U.T.I by 9% in groups I, 8% in group II and lastly other infection by 6% & 5% in group I and II respectively. Higher total bilirubin, serum creatinine and blood urea, severity and size of varices as (42%, 29%) of group I have Large V, FV respectively versus (27%, 7%) in group II ,postsclerotherapy ulcer, higher portal vein pressure and PVT as (10%) of group I have PVT versus (3%) of group II , massive blood transfusion (more than 4 units). Mortality rate was higher in group I as (8%) of patients died versus (1%) in group II. *Conclusions:* Variceal rebleeding is mainly associated with:, advanced liver disease (Child C), the volume of ascites, higher total bilirubin, serum creatinine and blood urea, severity and size of varices. postsclerotherapy ulcer ,higher portal vein pressure and PVTH , presence of infection and massive blood transfusion.
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1.Introduction:

Cirrhosis is the most advanced form of liver disease and variceal bleeding is one of its frequent and lethal complications. Over half of the patients with cirrhosis will develop varices. The risk of bleeding once EV is formed is 20% to 35% within 2 years. The reported mortality rate from first episode of variceal bleeding is 17% to 57%.[1]

The American association for the study of liver disease single topic symposium stated that cirrhotic patients should be screened for the presence of EV when portal hypertension is diagnosed . It had been suggested for endoscopy to be repeated at 2-3 years interval in patients without varices and at 1-2years interval in patients with small varices to evaluate the development and or progression of EV[2]. Cirrhotic patients with acute variceal bleeding are characterized by a high mortality and considerable rebleeding rate. Although therapeutic approaches including pharmacological treatment, injection sclerotherapy, band ligation and transjugular intrahepatic Porto-systemic shunt (TIPS) have been developed to prevent rebleeding, mortality in these patients' remains as high as 30%–50%. Reports showed that early rebleeding ranged from 30% to 40% within the first 6 weeks, and was significantly associated with the risk of death within 6 weeks . So exploring predictors of rebleeding is very important for cirrhotic inpatients[3,4].

Upper gastrointestinal (GI) bleeding is common, costly, and potentially life threatening. It must be managed promptly and appropriately to prevent adverse outcomes. More people are admitted to the hospital for upper GI bleeding than for congestive heart failure or deep vein thrombosis. Despite advances in therapy, the case-fatality rate has remained unchanged at 7% to 10%[5]. This may be because today's patients are older and have more comorbidities than those in the past[6].

Causes of upper bleeding :

Variceal bleeding mostly due to liver disease accounts for a large percentage of upper GI bleeding, the mortality rate from a single episode of variceal bleeding is30%, and 60% to 70% of patients die within 1year.

Peptic ulcer; Fortunately, up to 80%of bleeding ulcers stop bleeding spontaneously without any intervention[7,8], Gastro duodenal erosions account for about 12%, Less frequent causes include Mallory Weiss tears, erosive duodenitis, Dieulafoy ulcer (a type of vascular malformation), other vascular lesions, neoplasms, aortoenteric fistula, and gastric antral vascular ectasia.

Varices

Varices are abnormal distended veins usually in the esophagus (esophageal varices) Fig1 and less frequently in the stomach (gastric varices) or other sites (ectopic varices) usually occurring as a consequence of liver disease. Bleeding is characteristically severe and may be life threatening.

The size of the varices and their propensity to bleed is directly related to the portal pressure, which, in the majority of cases, is directly related to the severity of underlying liver disease. Large varices with red spots are at highest risk of rupture.

The mechanisms underlying rupture of esophageal varices are poorly defined. It has been demonstrated that the portal pressure is usually >10mmHg in patients who develop esophageal varices and the portal pressure generally exceeds12mmHg in patients with rupture of varices. Portal hypertension, a major hallmark of cirrhosis, is defined as a portal pressure gradient exceeding 5 mm Hg[9].

The mechanism of the increase in portal pressure depends on the site and the cause of portal hypertension, cirrhosis being the most common cause in the Western world[6].

The initial event in the development of portal hypertension in cirrhosis is an increase in resistance to outflow from the portal venous bed. This results are from a relatively fixed component from distortion of the intrahepatic vascular bed from the disruption of hepatic architecture and a dynamic component from impaired intrahepatic vasodilation. An estimated 30% of the increased portal resistance is due to the hemodynamic changes, characterized by hepatic vasoconstriction and impaired response to vasodilatory stimuli[10,11].

An intrahepatic decrease in the production of the vasodilator nitrous oxide (NO)[12], in combination with an increase in the production of the vasoconstrictor endothelin-1, is the major contributor to the dynamic increase in hepatic vascular resistance[13, 14] Cirrhosis is associated with hyperdynamic circulatory state that is characterized by peripheral and splanchnic vasodilation, reduced mean arterial pressure, and increased cardiac output. NO-mediated[15].

Splanchnic vasodilatation produces an increase in inflow of systemic blood into the portal circulation, which causes an increase in portal pressure[16]. Portal pressure is most commonly determined by the hepatic vein pressure gradient (HVPG), which is the difference between the wedged hepatic venous pressure (reflecting the hepatic sinusoidal pressure) and free hepatic vein pressure[17]. In combination with venography, right-sided heart pressure measurements, and transjugular liver biopsy, measurement of the HVPG usually delineates the site of portal hypertension (i.e., presinusoidal, sinusoidal, or postsinusoidal).

Diagnosis of varices

Upper gastrointestinal endoscopy: It is the most common method to diagnose varices[18].

Endoscopic ultrasound (EUS): Has been used to study esophageal varices and to identify a high risk of bleeding by assessment of the cross-sectional area of varices[19].

Esophageal capsule endoscopy: It is a promising modality to assess varices.It may provide an accurate, less invasive alternative to EGD for the detection of esophageal varices or portal hypertensive gastropathy[20].

Variceal Rebleeding

Recurrent bleeding was defined as any episode of upper gastrointestinal tract bleeding that occurred after the first sclerotherapy session or subsequent between scheduled treatment sessions. The time frame of variceal rebleeding can be divided into very early rebleeding (within 5 days of acute bleeding), early rebleeding(within 6 weeks of acute bleeding) and late rebleeding. Once acute variceal bleeding is controlled, prevention of recurrent bleeding should be emphasized.

Factors affecting risk of continued bleeding or recurrent bleeding and associated with failure to control acute hemorrhage

Spurting varices, Hhigh Child-Pugh score, high hepatic venous pressure gradient, infection, and Portal vein thrombosis.

Factors associated with early rebleeding

Severe initial bleeding, overly aggressive volume resuscitation, infection, high hepatic venous pressure gradient, complications of endoscopic therapy, and renal failure.

Factors associated with late rebleeding

High Child-Pugh score, large variceal size, and continued alcohol use[21-23].

2. Patients and Methods

This study was conducted on cirrhotic patients who were admitted to Tanta University Hospital , Internal Medicine Department because of variceal bleeding.

These patients were divided into 2 groups:

Group I: 100 Cirrhotic patients presented with rebleeding after previous endoscopic treatment of known varices within 6 weeks of acute bleeding. **Group II:** 100 Cirrhotic patients who were admitted with variceal bleeding and on regular follow up didn't develop early or late rebleeding in regular follow up session. ***Patients were subjected to:*** Careful drug, history and transfusion requirement in the previous bleeding. Routine laboratory investigation including: Liver function tests, Complete blood count,blood urea,Serum creatinine, ascetic fluid analysis, Urine analysis, Chest x ray, abdominal and pelvic ultrasonography.

Informed consent was taken from all patients for practical work. Any unexpected risks appear during the course of the research was cleared to the participants and the ethical committee on time

Exclusion criteria: Non-cirrhotic patients

3. Results

In this study 71 % of population were males and 29 % females. The mean age of group I was 57.37 years while 55.84 years in group II. Comparison between both studied groups as regard age and sex showed no statistical significant values. (Table 1).

Table (1): Demographic data of both groups

Demographic data		Groups		
		Group I	Group II	*P*-value
Male	N	73	69	0.533
	%	73.00	69.00	
Female	N	27	31	
	%	27.00	31.00	
Age	Mean	57.37	55.84	0.298

As regard past medical history; 41 % of group I were diabetics versus 30% in group II and 3 % were hypertensive in group I versus 10% in group II.

Comparison between both groups was significant as regard blood pressure with [*P*-value 0.045*] so meaning more hypotensive patients in group I but non- significant as regard diabetes. (Table 2).

Table (2): Past medical history of both groups

Medical diseases			Groups		
			Group I	Group II	*P*-value
Blood pressure	HTN	N	3	10	0.045*
		%	3.0	10.0	
	Hypotension	N	97	90	
		%	97.0	90.0	
Diabetes	N		41	30	0.104
	%		41.00	30.00	

As regard Child classification of the studied patients ;11 % of our patients in group I were Child A, 22% Child B and 67% Child C versus 20%, 49% and 31% respectively in group II. Comparison between both groups was significant with [*P*-value <0.001*]. (Table 3).

Table (3): Child classification of both groups

Child Class		Groups		
		Group I	Group II	Total
A	N	11	20	31
	%	11.00	20.00	15.50
B	N	22	49	71
	%	22.00	49.00	35.50
C	N	67	31	98
	%	67.00	31.00	49.00
Total	N	100	100	200
	%	100.00	100.00	100.00
Chi-Square	X2	26.105		
	P-value	<0.001*		

The mean transfusion units of group I was 2.950 ± 1.282 while 2.450 ± 1.226 in group II. Comparison between both studied groups as regard blood transfusion showed statistically significant difference with [*P*-value 0.005]. (Table 4).

Table (4): Comparison between both groups as regard number of units of blood transfusion

Groups	Number of units of blood received						T-Test	
	Range			Mean	±	SD	t	*P*-value
Group I	1.000	-	6.000	2.950	±	1.282	2.819	0.005
Group II	1.000	-	6.000	2.450	±	1.226		

Analysis of studied risk factors associated with rebleeding showed significant increase with infection in group I compared with group II with [*P*-value0.000] included chest infection by 38% in group I, 11% in group II.S.B.P by 15% in group I ,6% in group II . U.T.I by 9% in groups I, 8% in group II and lastly other infection(gastroentritis ,cellulitis, and wound infection) in groups I and II by 6%, 5% respectively. (Table 5).

There was no statistical difference between both groups as regard smoking, use of NSAIDs and compliance to B blockers.

Table (5): Comparison between both groups regarding infection

Infection	Group I		Group II		Total	
	N	%	N	%	N	%
No infection	39	39.00	70	70.00	109	54.50
Chest infection	38	38.00	11	11.00	49	24.50
S.B.P	15	15.00	6	6.00	21	10.50
U.T.I	9	9.00	8	8.00	17	8.50
Others	6	6.00	5	5.00	11	5.50
X^2	31.821					
P-value	0.000					

Others mean infection such as gastroenteritis, cellulitis and wound infection.

The statistical analysis of laboratory investigations showed significant difference with total serum bilirubin, serum creatinine and blood urea with [*P* value<0.001, 0.026 and <0.001] respectively while no significant difference between both groups as regarding platelets count, serum albumin and prothrombin time. (Table 6).

Table (6): Laboratory data of both studied groups

Item	Group I	Group II	T test	
			t	*P*value
Platelets count				
Range	20.000 -880.000	20.000-210.000	1.560	0.120
±SD	±107.844	±36.968		
Mean	96.424	78.630		
Prothrombin time (seconds)				
Range	12.400 -27.000	12.000 -22.000	1.729	0.085
±SD	±2.436	±2.231		
Mean	16.781	16.210		
Total serum bilirubin (mg/dl)				
Range	0.400 -26.000	0.700 -18.000	4.210	<0.001*
±SD	±4.954	±3.081		
Mean	6.205	3.749		
Serum albumin (mg/dl)				
Range	18.000 -44.000	19.000 -32.000	0.762	0.447
±SD	±4.760	±3.822		
Mean	26.425	26.890		
Serum creatinine (mg/dl)				
Range	0.600 - 6.000	0.600 - 4.000	2.236	0.026*
±SD	±0.874	±0.704		
Mean	1.602	1.351		
Blood urea (mg/dl)				
Range	19.300 -240.000	25.000 -145.000	4.561	<0.001*
±SD	±38.559	±23.191		
Mean	79.623	59.100		

The statistical analysis of ultrasound finding of both groups was significant with amount of ascites, portal vein diameter and patency with [*P* value<0.001, <0.001 and 0.045] while non- significant with liver parenchyma ,presence of hepatic focal lesion and splenic diameter. (Table7).

Table (7): Ultrasound finding of both groups

Item		Group I	Group II	Total	Chi-square	
					X2	*P* value
Focal lesion						
No F.L	N	79	86	166	2.174	0.140
	%	79%	86%	83%		
Focal lesion	N	21	13	34		
	%	21%	13%	17%		
Portal vein diameter (mm)						
Range		13.7-18	11-18	----------		*<0.001*
Mean		15.83	15.25			
±SD		0.962	1.48			
Portal vein patency						
Patent PV	N	90	97	187	4.031	0.045*
	%	90%	97%	93.5%		
Portal vein Thrombosis	N	10	3	13		
	%	10%	3%	6.5%		
Spleen diameter (cm)						
Range		13-23	11.8-22	----------		0.886
Mean		16.789	16.739			
±SD		2.114	2.010			
Amount of ascites						
No ascites	N	9	13	22	42.40	<0.001*
	%	9%	13%	11.06%		
Mild	N	18	51	69		
	%	18%	51%	34.67%		
Moderate	N	23	26	49		
	%	23%	26%	24.62%		
Massive	N	49	10	59		
	%	49%	10%	29.65%		

Analysis of endoscopic finding of both groups was significant as regard FV, large V and post sclerotherapy ulcer in group I and small V in group II with [*P*-value0.0001 / 0.037 / 0.000 / 0.001 respectively], while non-significant with PHG, Gastroesophageal V (GOV) and post band ligation ulcer. (Tables 8-11).

Table (8): Classification of V of both groups

Grade	Group I		Group II		Total		Chi-square	
	N	%	N	%	N	%	X^2	*P*-value
Small .V	44	44.00	67	67.00	111	55.50	9.799	0.001*
Large .V	42	42.00	27	27.00	69	34.50	4.337	0.037*
GO.V	7	7.00	3	3.00	10	5.00	0.947	0.330
FV	29	29.00	7	7.00	36	18.00	14.939	0.0001*

Table (9): Comparison between both groups regarding post sclerotherapy ulcer

Post sclerotherapy ulcer		Group I	Group II	Total
Negative	N	79	96	175
	%	79.00	96.00	87.50
Positive	N	21	4	25
	%	21.00	4.00	12.50
Total	N	100	100	200
	%	100.00	100.00	100.00
Chi-square	X^2	14.328		
	P-value	0.000		

Table (10): Comparison between both groups regarding post band ligation ulcer

Post band ligation ulcer		Group I	Group II	Total
Negative	N	98	99	197
	%	98.00	99.00	98.50
Positive	N	2	1	3
	%	2.00	1.00	1.50
Total	N	100	100	200
	%	100.00	100.00	100.00
Chi-square	X^2	0.345		
	P-value	0.557		

Table (11): Comparison between both groups regarding PHG

PHG		Group I	Group II	Total
Negative	N	84	88	172
	%	84.00	88.00	86.00
Positive	N	16	12	28
	%	16.00	12.00	14.00
Total	N	100	100	200
	%	100.00	100.00	100.00
Chi-square	X^2	0.666		
	P-value	0.414		

As regard prognosis during the period of hospital admission, 82 % of our study population improved while 13.5% developed hepatic encephalopathy and 4.5 % died. Comparison between both groups were significantly higher in group I regarding morbidity and mortality with[P-value 0.018*]. (Table 12).

Table (12): Prognosis during hospital admission

Prognosis		**Groups**		
		Group I	**Group II**	**Total**
Improved	**N**	76	88	164
	%	76.00	88.00	82.00
Hepatic encephalopathy	**N**	16	11	27
	%	16.00	11.00	13.50
Died	**N**	8	1	9
	%	8.00	1.00	4.50
Chi-Square	**X^2**	8.008		
	***P*-value**	0.018*		

4. Discussion

Cirrhosis is the most advanced form of liver disease and variceal bleeding is one of its frequent and lethal complications. Over half of the patients with cirrhosis will develop varices. The risk of bleeding once EV is formed is 20% to 35% within 2 years. The reported mortality rate from first episode of variceal bleeding is 17% to 57%[1].

Cirrhotic patients with acute variceal bleeding are characterized by a high mortality and considerable rebleeding rate. Although therapeutic approaches including pharmacological treatment, injection sclerotherapy, band ligation and transjugular intrahepatic Porto-systemic shunt (TIPS) have been developed to prevent rebleeding, mortality in these patients' remains high [3]. So exploring predictors of rebleeding is very important for cirrhotic inpatients.

Analysis of the clinical results of the present work revealed that there was no significant difference among our patients groups regarding age and gender, these results are in agreement with **Lee**,[24] who revealed that age and gender had no significant influence on the incidence of rebleeding but on the other hand they disagreed with our study as regard blood pressure as it had a significant difference between the study groups. In group I 97% have low blood pressure and this may reflect severe illness, severity of bleeding and advanced liver disease. This study provides evidence that rebleeding after initial EV bleeding in cirrhotic patients was significantly associated with, Child-Pugh grade C (67% of group I belong to child C) and higher total-bilirubin. This was consistent with the study performed by Wang,[3] and Nagib,[25] who stated that rebleeding is positively correlated to severe hepatic dysfunction (Child's class C).

Our results showed that rebleeding was significantly associated with elevated serum creatinine and blood urea levels and this was in agreement with Wang,[3] who stated that rebleeding occurred more with patients with higher creatinine. In the opposite Lee,[24] reported that laboratory data was not a risk factor for rebleeding. Renal impairment can results from hypovolemic state associated with severe bleeding; in the other hand renal impairment may cause coagulopathy.

Comparison between different groups regarding ascites shows statistically significant difference. In our study 49% of group I have massive ascites versus 10% in group II. Massive ascites was a risk factor for rebleeding after EST as in several other studies Feng,[26] , who demonstrated that a moderate to excessive volume of ascites was a predicting factor for post-EST bleeding. This may be explained by; the elevated portal vein pressure results in a larger volume of ascites.

It was reported in our study that variceal bleeding recurred more in patients with large portal vein diameter and portal vein thrombosis, this is reported also by Feng,[26] and Nagib,[25] who demonstrating that rebleeding was more frequent in patients PVTH. This might be due to higher basal portal vein pressure.

Our results also showed positive correlation between infection and rebleeding specially chest infection followed by SBP (38% of group I have chest infection and 15% have SBP).These results are in agreement with Liao,[27] that reported that severe cough (chest infection) increase intravariceal pressure and susceptibility for bleeding. Lee,[24] reported that infection have a positive correlation with rebleeding. This may be due to bacterial infections and/or endotoxaemia that 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.

Comparison between the two groups as regard blood transfusion showed a significant value in blood transfusion requirement in group I. This is reported by Wang & Liu[3], Nagib,[25] who stated that massive blood transfusions (more than 4 units) associated with variceal rebleeding in cirrhotic patients. In opposite to Lee,[24] who reported that blood transfusion is not a risk factor for variceal rebleeding. Massive blood transfusion was reflecting the severity of initial bleeding, more severe pathology and more liability for recurrent bleeding. Fluid expansion increases the splanchnic blood flow resulting in high portal blood pressure and higher rebleeding rate.

In our study we found that nonselective beta blockers intake was not a risk factor of rebleeding .In the other hand, Yen,[28], showed that the use of these drugs reduces the re-bleeding risk in 1 year from 60 to 42%. This controversy can be explained as follow, inadequate dose to obtain therapeutic results or the healthcare provider discontinues ß-blockers because of the side effects.

Currently, only invasive methods can identify responders. Instead, adequate endpoints of ß-blocker therapy are monitored noninvasively by heart rate and blood pressure reduction. While this is not always an indication of being a responder, it is easy, noninvasive, and the most accepted method to date. In spite of the documented need to reduce heart rate by 20%–25% with ß-blocker therapy, healthcare providers are not reaching this endpoint or just not prescribing the medications.

Results of this work showed that NSAIDs was not a risk factor for rebleeding as 91% of group I

don't use it versus 85% in group II. This can be explained by growing awareness to NSAIDs side effects.

In this study, comparison between the two study groups regarding endoscopic findings showed statistically significant difference regarding presence of FV and large EV.

In our study 29% of group I have FV versus 7% of group II and 42% with large V in group I versus 27% in group II. This result is in concordance with Nagib,[25] that stated that large size of varices is a risk factor for variceal bleeding.

Our results also showed that, there was significant difference among both groups regarding post sclerotherapy ulcers in endoscopic findings as there was 21% of group I suffering from it versus 4% of group II and we can explain this results as follow: Advanced liver disease in group I.Bad general condition.High incidence of infection and Different sclerotherapy techniques.

Joaquin,[29] explained that post sclerotherapy ulcer is a hazardous complication to sclerotherapy and it is usually due to an extensive wall necrosis induced by an incorrect injection technique, too much sclerosant being injected, or a high concentration of the sclerosant. Esophageal ulcers are common and they may cause bleeding in 20% of patients.

From this work, we found that variceal rebleeding was associated with increased incidence of encephalopathy and death as 8% of group I died versus 1% of group II, 18% with encephalopathy versus 11%in group I and II respectively. This is in concordance to Yen,[28] who stated that the short-term mortality in recent series remained approximately 15–20%.

Conclusion

From the previous results it's clear that the variceal rebleeding is mainly associated with:Advanced liver disease (Child C).The volume of ascites.Higher total bilirubin, serum creatinine and blood urea. Severity and size of varices. Postsclerotherapy ulcer.Higher portal vein pressure and PVTH.Presence of infection. Massive blood transfusion.

Recommendations

From the previous results we can recommend the following: Always consider infection in recurrent bleeding even if no apparent clinical clues.Prevention of infection :a) Pneumococcal and influenza vaccines.b) Prophylaxis for S.B.P.Detection and proper management of PVTH. Avoid massive blood transfusion (the goal to reach by HB to 9 gm. /dl).

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