Potential Precipitating Factors of Variceal Bleeding

Gamal F. El Naggar, Mahmod F. Selim, Atef M. Taha, Nashwa M. Nor Eldin, Loai M. Elahwal, Khalid Z. Darwish, Ahmed A. Abo omar

Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract: Background and study aim: Variceal bleeding accounts for 10-30% of upper gastrointestinal haemorrhage and is a major cause of death in patients with cirrhosis. The incidence of chronic liver disease and hence portal hypertension in Egypt is exceptionally high, maintaining the highest prevalence of hepatitis C virus (HCV) worldwide, bilharzial periportal fibrosis as well as rising rates of hepatocellular carcinoma (HCC). In this work, we prospectively studied the potential precipitating factors for variceal bleeding in Middle Delta, Egypt. **Patients and methods:** Four hundred consecutive patients with liver cirrhosis who presented to Tanta University Hospital, from April 2011 till October 2011 with endoscopy documented acute variceal bleeding were invited to participate in the study. Our patients were classified into: **Group I:** 400 Patients with liver cirrhosis and acute variceal bleeding. **Group II**: 50 Matched patients with same Child-Pugh class and esophageal varices without bleeding (As a control group). All patients included in the study will be subjected to full history taking with a standard questionnaire regarding constipation, vomiting, cough, and other potential risk factors. **Result:** Vomiting, constipation and sever cough showed significant statistical increase in bleeding patients than the control group. (*P.* value < 0.05). The relation between the constipation and vomiting and the recurrence of bleeding was statistically significant. (*P* value < 0.05). **Conclusion**: Straining activities and infection could precipitate variceal bleeding episode. Routine vaccination, proper management of infection will reduce bleeding and rebleeding episode in cirrhotic patients with varices.

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Key words: Precipitating factors, variceal bleeding, Cough, constipation, infection

1.Introduction

Upper gastrointestinal bleeding (UGIB): remains a significant source of mortality for both emergency admissions (11%) and inpatients (33%) [(1)].

Variceal bleeding accounts for 10-30% of upper gastrointestinal haemorrhage and is a major cause of death in patients with cirrhosis (2).

At the time of diagnosis of cirrhosis, esophageal varices are present in about 60% of decompensated and 30% of compensated patients (3).

The incidence of chronic liver disease and hence portal hypertension in Egypt is exceptionally high, maintaining the highest prevalence of hepatitis C virus (HCV) worldwide, bilharzial periportal fibrosis as well as rising rates of hepatocellular carcinoma (HCC) (4).

Two theories have been proposed to explain variceal bleeding.The erosion hypothesis proposed that variceal hemorrhage resulted from an external trauma eroding the thin and fragile wall of the varices. Esophagitis and subsequent ulceration were the most commonly suggested erosives (5).

At present, most authors accept the explosion hypothesis that suggests that

the main factor leading to rupture of the varices is the increased hydrostatic pressure inside the varix and its ensuing consequences, increasing variceal size and decreasing the thickness of its wall (6).

Several studies had discussed risk factors for variceal bleeding including clinical, endoscopic and hemodynamic parameters.

The Northern Italian Endoscopic Club (NIEC) showed that there was a strong correlation between a patient's Child class at the time of endoscopy and the rate of bleeding during follow up (7).

In this work, we prospectively studied the potential precipitating factors for variceal bleeding in Middle Delta, Egypt.

2. Patients and Methods

Four hundred consecutive patients with liver cirrhosis who presented to Tanta university hospital, from April 2011 till October 2011 with endoscopy documented acute variceal bleeding were invited to participate in the study.

Our patients were classified into:

Group I: 400 Patients with liver cirrhosis and acute variceal bleeding.

Group II: 50 Matched patients with same Child-Pugh class and esophageal varices without bleeding (As a control group)

An informed consent was taken from all participants after explanation the study design and all procedures were approved by Faculty of Medicine Research Ethics Committee (REC).

Exclusion criteria:

All contraindications of upper gastrointestinal endoscopy as:
-Shock
-Disturbed conscious level.
-Refusal of procedure
All patients included in the study will be subjected to:
-Full history taking with a standard questionnaire regarding constipation, vomiting, cough, and other potential risk factors.
(A) Constipation:
Constipation was defined according to the modified Rome II criteria (8) and was diagnosed if subjects had at least two of the following constipation symptoms in the week directly preceding the study: straining, lumpy or hard stool, sensation of evacuation or manual maneuvers to facilitate defecation during at least 25 % of defecations or fewer than three defecations per week.
(B) Cough:
Considered, if cough is present at least for 1 week before bleeding. Severity of the cough was classified as
- (0) Not at all
- (1) Mild, but the subject participated in normal daily activity
- (2) Moderate and the subject had decreased daily activity due to cough
- (3) Severe with a poor ability to sleep due to cough (9).
(C) Vomiting:
Vomiting was scored from 0 to 4
- (0) was defined as no vomiting.
- (1) was one episode of vomiting per day.
- (2) was two to five episodes per day.
- (3) was six to 10 episodes per day.
- (4) was defined as more than 10 episodes per day and requiring parenteral support (10).
(D) NSAID consumption:
If the patient have a history of taking NSAID in the week preceding bleeding (11).
-Complete clinical examination.
All patients included in the study will be subjected also to:
-Laboratory investigations including:
1-Complete blood count.
2-Liver function tests:
a) Serum albumin
b) ALT, AST.
c) Bilirubin.
3-Prothrombin time and activity.
4-Serum urea and creatinine.
5-Urine analysis.
6-Diagnostic aspiration of ascitic fluid
-Upper endoscopy:
Precautions;
-Short acting anesthesia (as Midazolam)
-Patient is fasting 8hours before endoscopy
-Imaging including:
1-Chest X –ray
2-Pelviabdominal ultrasound.
(Regarding spleen size, portal hypertension and collaterals)

We compared constipation, vomiting, and cough in 450 patients with and without evidence of bleeding using a standard questionnaire that allowed reliable, reproducible measurement of these symptoms.

Statistical analysis

Statistical analysis of this study was conducted, using the mean, standard deviation, and chi-quare test by (SPSS 13.0, SPSS Inc., Chicago, IL).

3. Results

Table (1): Base line characteristics of patients according to age, sex and Child Classification

Character	Group I (n=400)	Group II (n=50)	*P*.value
Sex(men\women) Percentage	(269\131) (67.3♂-32.8♀)	(35\15) (50♂-50♀)	0.252 Chi-Square X^2=0.417
Age in years	53.31±11.06	51.04±8.93	0.325 t.test
Child classification A\B\	25\124\251	16\14\20	0.001* Chi-Square

***Significant (*P*<0.05)**

Table (2): Comparison between both groups as regard to endoscopic findings: It was statistically significant (*P*.value = **0.001**) in group I as regard to size of varices

Endoscopy findings		Group I (n=400)	Group II (n=50)
Grade(I) Esophageal varices (O.V)	N	46	15
	%	11.5%	30.0%
Grade(II) O.V	N	157	23
	%	39.3%	46.0%
Grade(III) O.V	N	82	6
	%	20.5%	12.0%
Grade(IV) OV	N	57	3
	%	14.3%	6.0%
Fundal varieces	N	25	3
	%	6.3%	6.0%
Post sclerotherapy ulcer	N	33	-
	%	8.3%	-
Chi-Square	X^2	19.325	
	P-value	0.001*	

Analysis of constipation

Comparison between both groups as regard to constipation showed increase constipation in group I

which is statistically significant. (*P*.value: 0.041), (Odd ratio: 0.767).

Table (3): Comparison between both groups as regard to constipation

Constipation		Group I	Group II
Patients with constipation	N	70	7
	%	17.5%	14%
Patients without constipation	N	330	43
	%	82.5%	86%

Relation between constipation and child classification

Relation between constipation and Child classification was statistically significant in both groups.

Table (4) Relation between constipation and child classification

	CONSTIP GI		CHILD A	CHILD B	CHILD C
	Yes	N	8	12	50
		%	32.0%	9.7%	19.9%
	No	N	17	112	201
		%	68.0%	90.3%	80.1%
	Chi-Square	X^2	9.915		
		P-value	0.007		

*Significant (*P*<0.05)

	CONSTIP GII		CHILD A	CHILD B	CHILD C
	Yes	N	-	2	5
		%	-	14.3%	25.0%
	No	N	16	12	15
		%	100.0%	85.7%	75.0%
	Chi-Square	X2	4.616		
		P-value	0.085		

*Significant (*P*<0.05)

Table (5): Relation between constipation and attack of bleeding

Constipation in Group I		ATTACK 1st	ATTACK Recurrent Bleeding
Yes	N	33	37
	%	47.1%	52.9%
No	N	185	145
	%	56.1%	43.9%
Chi-Square	X^2	2.558	
	P-value	0.047* (significant)	

Analysis of vomiting

Group I patients showed statistically significant increase in the incidence and severity of vomiting in comparison with group II. (*P*.value:0.029), (Odd ratio: 1.22).

Table (6): Comparison between both groups as regarding to vomiting

VOMITING		Group GI	Group GII
0	N	328	48
	%	82.0%	96.0%
1	N	1	-
	%	0.3%	-
2	N	70	2
	%	17.5%	4.0%
3	N	1	-
	%	0.3%	-
Chi-Square	X^2 8.623		
	P-value 0.029 * Significant		

0: no vomiting, 1: one episode per day,2: two to five attack per day,3:six to ten episodes per day.

Relation between vomiting and Child classification was non significant (*P*.value=0.062 in group I &0.523 in group II).

Relation between the vomiting and the attack of bleeding

There was statistical significance in the rebleeding subgroup. (*P*.value:0.014)

Table (7): Relation between the vomiting and the attack of bleeding

VOMITING in Group I		ATTACK 1st	ATTACK Recurrent
No vomiting	N	179	149
	%	54.6%	45.4%
Mild vomiting	N	1	-
	%	100.0%	-
Moderate vomiting	N	38	32
	%	54.3%	45.7%
Severe vomiting	N	-	1
	%	-	100.0%
Chi-Square	X^2		4.595
	P-value		0.014

Analysis of cough

When classifying cough into grades, patients with severe cough were noted to be larger in number and statistically significant in group I, but the overall incidence of cough was non significant.), (Odd ratio: 1.339).

Statistical analysis showed no correlation between cough and age or cough and recurrence of bleeding.

Relation between cough and Child classification was non significant but from 112 patients of group II had cough,5 patients were Child A, 31 Child were B and 76 were Child C.

Table (8): Comparison between both groups regarding cough

Cough		Group I	Group II	P value
0 (Not at all)	N	288	41	0.014
	%	72.0%	82.0%	
1 (Mild)	N	21	2	0.048
	%	5.3%	4.0%	
2 (Moderate)	N	73	6	0.009
	%	18.3%	12.0%	
3 (Severe)	N	18	1	0.001
	%	4.5%	2.0%	

Table (9): Relation between cough and attack of bleeding

Cough Group I		ATTACK	
		1st	Recurrent
0 Not at all	N	157	131
	%	72.0%	72.0%
1 Mild	N	9	12
	%	4.1%	6.6%
2 Moderate	N	44	29
	%	20.2%	15.9%
3 Severe	N	8	10
	%	3.7%	5.5%
Chi-Square	X^2	2.863	
	P-value	0.099	

Analysis of infections

In our study population 179 patients had infections (59 had chest infection, 61 had SBP and 59 had UTI). And 271 patients had no infection

Comparison between both groups as regarding presence of infection show non statistical significant in group I in comparison with group II, Although numerically increase in group I.(*P*.value:0.418),(Odd ratio:1.119).

Table (10): Comparison between both groups as regarding presence of infection

Infection		Group	
		I	II
No Infection	N	236	35
	%	59.0%	70.0%
Chest Infection	N	56	3
	%	14.0%	6.0%
SBP	N	56	5
	%	14.0%	10.0%
UTI	N	52	7
	%	13.0%	14.0%
Chi-Square	X^2	3.265	
	P-value	0.418	

Analysis of NSAID use

In our study 71 patients use NSAID (63 in group I and 8 in group II) while 379 patients are non NSAID users.

Comparison between both groups as regarding consumption of NSAID show no statistical significance. (*P*.value= 0.584), (Odd ratio:1.119).

Table (11): Comparison between both groups as regarding consumption of NSAID

NSAID Consumption		Group	
		GI	GII
Yes	N	63	8
	%	15.8%	16.0%
No	N	337	42
	%	84.3%	84.0%
Chi-Square	X^2	0.023	
	P-value	0.584	

4. Discussion

Esophageal varices (EV) are a serious consequence of portal hypertension. (12).

Variceal bleeding is the last step of a chain which is initiated by an increased portal pressure, followed by the development and progressive dilation of varices, until they finally bleed. (6).

The stage of cirrhosis, with impairment of hemostasis, will directly influence the gravity of hemorrhage; the hepatic venous pressure higher than 12 mm Hg will induce the increase of the bleeding risk (13,14).

This study was designed to determine the potential risk of Valsalva maneuver-related activities, infection and NSAID in precipitating variceal bleeding.

The Valsalva maneuver causes an abrupt increase in variceal pressure (15), which can induce EV bleeding. Increase in intra-abdominal pressure markedly increase azygous blood flow, an index of gastroesophageal collateral blood flow, and markedly increase variceal pressure and tension (16,17).

Effect of seasonal variation on acute upper gastrointestinal bleeding and etiology including variceal bleeding was demonstrated in several studies.

Many factors might contribute to that variation, including drug usage, chest infections and climate changes (18).

In this work we have tried to study different risk factors that could explain this observation. We compared constipation, vomiting, and cough in 450 patients with and without evidence of bleeding. Constipation, vomiting, and cough were assessed using a standard questionnaire that allowed reliable, reproducible measurement of these symptoms.

In this study, vomiting and constipation showed significant statistical increase in bleeding patients than the control group. (*P*.value: < 0.05). However, comparison between both groups regarding cough was statistically non significant, because a subgroup of group II was complaining of respiratory infection, so

cough was prevalent among. However severe cough was significantly higher in group I. (*P* value< 0.05). The relation between the constipation and vomiting and the recurrence of bleeding was statistically significant. (*P* value< 0.05).

A similar study was conducted by Escorsell A *et al.* (15) who designed a study to verify the effects of elevations in intra abdominal pressure on variceal hemodynamics, assessed by measuring changes in variceal pressure, variceal volume, and variceal wall tension. Changes in variceal pressure were measured by using a noninvasive pressure-sensitive gauge developed in their laboratory that allowed reliable, reproducible measurements of variceal pressure.

They showed that increasing intra abdominal pressure results in a highly significant increase in variceal pressure and size.

Also, Staritz *et al.*.(19) showed that transient increases in intra abdominal pressure, such as those caused by the Valsalva maneuver, significantly increased intravascular esophageal variceal pressure.

Bacterial infection is deemed a crucial factor in triggering variceal bleeding and antibiotic prophylaxis can prevent bleeding and rebleeding.(20,21).

During bacterial infection and sepsis, the liver is exposed to a neutrophil mediated injury involving both hepatocytes and endothelial cells, which could release heparin-like substances into the systemic circulation. (22) Also, bacterial infections could lead to mast cell activation with the consequent release in the circulation of heparin and other mediators with anticoagulant activity (23).

A randomized controlled study by Hou MC *et al.* showed (24) showed that antibiotic prophylaxis prevent infection and rebleeding as well as decreased the amount of blood transfused in patients with acute variceal bleeding.

In our patients, infection was reported more frequent in patients with bleeding episodes than control group but not statistically significant (chest infection prevalence was higher than spontaneous bacterial peritonitis).

This can be explained by overlap between risk factors, progressive course of cirrhosis and its complication, delay in seeking medical advice and short duration of the study.

A study conducted by Yousif M *et al.* (25) to show role of endogenous heparinoids and bacterial infection in variceal bleeding, emphasize the importance of routine antibiotic prophylaxis in the setting of acute variceal bleeding in patients with liver cirrhosis to reduce the severity and duration of the episode and to decrease the risk of rebleeding.

NSAID induced mucosal damage probably results from a complex mechanism. Local mucosal injury and inhibition of cyclooxygenase type 1 activity lead to a reduction in mucosal defenses, restricted mucosal blood flow,(26) and gastric erosions, which may facilitate variceal rupture.

In our study, the difference in NSAID use between both groups was non significant, most likely due to the low prevalent use of NSAID in our study population, due to growing awareness of their risk, and physician advice against them. However, a study done by V De Lédinghen *et al.* (27) suggests that cirrhotic patients who use NSAIDs are about three times more likely to have a first variceal bleeding episode than cirrhotic patients who do not. The risk appeared to be due to aspirin mainly, alone or combined with other NSAIDs, only in patients with grade 2 or 3 varices.

In conclusion, severe cough and chest infection were significantly higher in cirrhotic patients with bleeding varices than non variceal bleeder.
Routine vaccination, proper management of infection will reduce bleeding and rebleeding episode in cirrhotic patients with varices.

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