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PREDICTIVE FACTORS OF BLEEDING RELATED TO POSTBANDING ULCER FOLLOWING ENDOSCOPIC VARICEAL LIGATION IN CIRRHOTIC PATIENTS: A CASE-CONTROL STUDY

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Original article

**PREDICTIVE FACTORS OF BLEEDING RELATED TO
POSTBANDING ULCER FOLLOWING ENDOSCOPIC VARICEAL
LIGATION IN CIRRHOTIC PATIENTS: A CASE-CONTROL STUDY**

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ABSTRACT

Background: Life-threatening bleeding due to early spontaneous slippage of rubber bands have been described after variceal ligation in cirrhotic patients.

Aims: To determine the predictive factors of this complication in cirrhotic patients.

Methods: Among 605 patients, 21 patients (mean age 56.6 ± 13.5 years) developed 23 spontaneous band slippages with bleeding on postbanding ulcer, as confirmed by endoscopy. Cirrhosis was alcoholic in 13 patients (62%), post viral hepatitis in 3 (14%) and from other causes in 5 (24%). A case-control study was performed comparing 17 from these patients who presented the complication after a first ligation with 84 of the 584 controls who underwent first endoscopic variceal ligation without bleeding complication.

Results: Bleeding occurred $13.5 \text{ days} \pm 7.3$ [2-29] following ligation. Eleven patients died following the bleeding complication (52%). Using a multivariate analysis, previous upper variceal digestive bleeding (OR 12.07, 95%CI [2.3-63.43]), peptic oesophagitis (OR 8.9, 95%CI [1.65-47.8]), high APRI score (OR 1.54, 95%CI [1.11-2.16]) and low prothrombin index (OR 0.54, 95% CI [0.31-0.94]) were independent predictive factors of bleeding.

Conclusions: Bleeding related to postbanding ulcer is a rare but severe complication. The proposed predictive factors should be looked for and minimized before variceal ligation.

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Key words: oesophageal variceal ligation, bleeding, cirrhosis, spontaneous slippage, rubber bands, postbanding ulcer.

INTRODUCTION

In spite of a more efficient approach to upper digestive bleedings over the past three decades, acute oesophageal variceal bleeding remains a severe and deadly complication in the cirrhotic patient life which marks a turning point in the evolution of their liver disease¹. In this context, endoscopic variceal band ligation (EVL) has been proposed as one of the best emergency as well as prophylactic haemostatic treatment. This approach has been recommended now by the consensus workshop in these different situations^{2, 3}. EVL is considered to be safe with few treatment-related complications⁴. Indeed, most frequently reported complications are minors with transient dysphagia or post ligation pain⁵. On the other hand, oesophageal stricture formations have only been reported in 1.9% of cases⁶.

Following EVL, a local ulcer is commonly found with a ensuing well described sequence of the pathological changes^{7, 8}. After strangulation, variceal thrombosis occurs with varying degrees of ischemic necrosis inducing detachment of the rubber band. Then a shallow ulcer usually occurs that heals within 2 to 3 weeks, allowing the development of fibrosis in the sub mucosa. In case of premature detachment of the rubber band, before variceal thrombosis, marked alterations of the mucosa can be seen with dilated variceal vessels in necrotic areas⁸. These pathological findings may explain the rare rebleeding episodes from oesophageal ulcerations following EVL⁷. Up to now only few reports of life-threatening bleeding due to early spontaneous slippage of rubber bands and post banding ulcer have been described⁹⁻¹¹. These reports were only dealing with case reports and no large study of this complication is available in cirrhotic patients treated by EVL.

The aim of this case-control study was to determine the predictive factors of bleeding from spontaneous slippage of rubber bands and post-EVL ulcer in cirrhotic patients.

MATERIALS AND METHODS

Study population

The characteristics of patients enrolled in this case-control study, are summarized in Table 1. Six hundred five cirrhotic patients who underwent 837 EVL in our unit from 2002 to 2007 were evaluated and their chart reviewed. “Cases” were defined as cirrhotic patients who developed a digestive bleeding related to ulceration after spontaneous slippage of rubber band following a first EVL performed in emergency or prophylactic situation. This bleeding was an active one (spurting or oozing) due to the ulceration induced by the previous EVL⁵⁻⁷, confirmed by an gastroscopy performed within 12 hours after the haemorrhage and without other causes of digestive bleeding (such as non variceal upper gastrointestinal bleeding, gastric antral vascular ectasia, gastro oesophageal variceal bleeding or rebleeding site on oesophageal varices). Using this definition, twenty-one (3%) patients (17 males and 4 females, mean age: 56.6 years \pm 13.5) presented 23 bleeding episodes following EVL in relation to ulceration after sliding of rubber band but only in 17 patients (81%) the haemorrhage developed following a first ligation (and in four patients (19%) following a second session of ligation) (Table 1). Two patients presented 2 episodes of bleeding. “Controls” were defined as patients who underwent a first EVL without any complication (EVL performed in emergency or prophylactic situations). Eighty-four controls (60 males and 24 females, mean age: 58.5 years \pm 13.1) were then selected from the 605 patients with an EVL in our unit, using a string of computer-generated random numbers in a 4:1 ratio and compared with cases. For the case – control study and statistical analysis, we only kept and compare the 17 “cases” who presented a bleeding episode after the first EVL with the “controls”. Patients gave written informed consent to the EVL procedure and authorized the use of their personal data. The variables were retrospectively collected on the computer data base and the medical records of the institution.

Endoscopic procedure for EVL

Five senior endoscopists from our unit (experience of more than 250 ligations) performed the EVL under general propofol-induced anaesthesia with or without tracheal intubation. The endoscopes used were adult gastroscope type Olympus GIF 160 (Olympus Medical Systems, Hamburg, Germany) or Fujinon EG-450WR5 (Fujinon Medical Systems, Willich, Germany). The same procedure of ligation was used for each patient: 1) grade 2 and 3 varices were identified during withdrawal of the endoscope following a complete gastric aspiration.; 2) bands were launched on varices (mean of 5.2 ± 2 , maximum 12) with the same device (4 or 6 shooter Saeed multiband ligator, Cook Medical Endoscopy, Limerick, Ireland) in an ascending way through the oesophagus. In case of EVL for emergency treatment (acute bleeding), a rubber band was launched on the bleeding varices (protocol used in our unit).

Following EVL, proton pump inhibitors (PPI) (esomeprazole, 40 mg per day) were administrated during at least 3 days in all patients. Food intake was allowed 12 hours following the endoscopic procedure in case of prophylactic EVL and at the discretion of the physician in case of EVL for acute bleeding.

Treatment of the bleeding related to postbanding ulcer after spontaneous slippage of rubber band

In all “case” patients octreotide (25 µg per hour) and PPI dose infusion (esomeprazole – 40 mg per day) during five days after the bleeding complication were given. All patients received prophylactic antibiotherapy (ofloxacin) and the gastroscopy was performed in the six first hours after admission. Cyanoacrylate endoscopic injections were performed in 10 patients (43%), five patients (24%) had oesophageal balloon tamponade (for uncontrolled and massive bleeding with haemodynamic deficiency) and two patients (14%) had an emergency transjugular intrahepatic portosystemic shunts (TIPSS).

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Statistical analysis

In univariate analysis, we compared cases and controls with Chi-square distribution or Fisher's exact test to assess significance between proportions, and with two samples Student t test to assess significance with quantitative data. In multivariate analysis, binary logistic regression models were applied with bleeding after the EVL as dependant variable. Variables significantly associated with bleeding (with a significance level of $p < .05$) and with a clinical relevance were selected for possible inclusion in multivariate logistic regression models. Relationships were assessed by adjusted odds ratio (OR) with 95% confidence interval (CI). Two-sided p values $< .05$ were considered statistically significant. We used SAS software (Enterprise Guide 4.1 for Windows) for all statistical analyses (S.A.S institute Inc., Cary, NC, USA).

RESULTS

Outcome of patient after bleeding related to postbanding ulcer following EVL

Results are summarized in table 2. The prevalence of the bleeding complication was of 2.74% (23 episodes among 837 EVL) that occurred with a mean delay of 13.5 ± 7.3 days (range 2-29). This complication was quite severe, 11 of the 21 patients (52%) dying within a few days and, in the majority of cases (5 patients), secondary to a sepsis (one spontaneous bacterial peritonitis, two pneumonia and two septicemia). Seven of the 11 patients who died, did not receive prophylactic antibiotherapy during the EVL session inducing the postbanding ulcer. In univariate analysis, the development of a sepsis during the evolution was the only predictive factor of the fatal outcome ($p = .03$).

Comparison between "cases" and controls

The clinical, biological and endoscopic data as well as the medical history between "cases" and controls are summarized in Tables 1, 3, 4 and 5. The severity of the liver disease was significantly higher in "cases" than in controls with a higher Child Pugh class ($p = .04$) and score (9.1 ± 2.6 versus 7.7 ± 2.2 , $p = .02$). The presence of peptic oesophagitis ($p = .02$), previous upper variceal digestive bleeding ($p = .02$), the prophylactic EVL condition ($p = .038$), a higher platelet ratio index (APRI score) ($p = .04$), fresh plasma transfusion ($p = .01$), a lower total bilirubin level ($p = .04$) and a lower prothrombin index ($p = .01$) and albumin ($p = .02$) were significantly associated with the occurrence of the bleeding complication in "cases".

There was a trend of reaching significant difference for ascites ($p = .06$) and higher ratio aspartate aminotransferase / alanine aminotransferase ($p = .07$) in "cases".

There was no difference between "cases" and controls regarding: the previous use of β -blockers, the post EVL PPI use during more than 3 days and post EVL sucralfate use; the presence of gastro oesophageal varices; the size of varices treated; the presence of red signs;

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3 the number of rubber bands launched; the occurrence of post EVL pain; the
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6 antibioprophylaxis; the performance of EVL in emergency or in primary or secondary
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8 prophylactic situation; neither with the presence of symptomatic anaemia and the duration of
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10 hospitalization.
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Multivariate analysis

Variables significantly linked in univariate analysis to the occurrence of the bleeding complication following EVL, were assessed by multivariate analysis (Data included in the model are presented in table 6). Logistic regression identified four independent variables predictive of bleeding on ulceration after spontaneous slippage of rubber band: previous upper variceal digestive bleeding (OR 12.07, 95%CI [2.3-63.43]), the presence of peptic oesophagitis (OR 8.9, 95%CI [1.65-47.8]), a high APRI score (OR 1.54, 95%CI [1.11-2.16]) and a low prothrombin index (OR 0.54, 95% CI [0.31-0.94]) (Table 4).

Because the prothrombin index appeared to be a predictive variable of the occurrence of the bleeding complication, a Receiver-Operator Characteristics (ROC) curve was constructed to determine if a threshold value could be calculated allowing the discrimination of patients with or without risk of developing bleeding on post EVL ulcer and the slippage of the rubber band (Figure 1). A threshold value below 45% had a sensitivity, a specificity, a positive predictive value (PPV) of 47%, 81%, and 12% respectively and a negative predictive value (NPV) of 67% (area under curve of 0.7).

DISCUSSION

This large case control study shows for the first time that bleeding on ulcer after early spontaneous slippage of rubber band post EVL is a serious complication. Four independent factors (previous upper variceal digestive bleeding, the presence of peptic oesophagitis, a high APRI score and a low prothrombin index) are predictive of this life threatening complication. Only a few case reports have been reported⁹⁻¹¹. Most of the previous studies on bleeding following EVL in cirrhotic patients focalized on the rebleeding condition and risks without specifying the site of the bleeding by endoscopy. In these studies the rate of rebleeding within 5 days was 15% and the mortality was 14% within 6 weeks^{12, 13}. In the present study, we have analysed only patients in whom an endoscopic evaluation confirmed that of the post EVL bleeding was due to an ulceration induced by the rubber band and its **spontaneous** slippage. The prevalence of this complication is low (2.74%) but the study confirms the severe outcome of these bleedings with a high rate of death (52%), mainly due to the development of a sepsis **responsible for the majority of death of the patients**. Bacterial infection has already been reported as a risk factor of rebleeding following EVL in a previous retrospective study, but the source of bleeding was not documented¹⁴. In the present study, the high mortality rate **is certainly** explained by the low rate of prophylactic antibiotherapy performed during the initial EVL procedure (62%), particularly at the beginning of the study: seven **out of eleven** patients who died did not receive this prophylactic antibiotherapy **which is actually recommended**².

The severity of the liver disease is an important factor in the occurrence of this bleeding complication. Low prothrombin index, high APRI score and previous upper variceal digestive bleeding appeared to be independent predictive factors of bleeding related to post EVL ulcerations. The poor liver condition (Child Pugh C class, high MELD score) have been previously well identified as predictive factors of rebleeding in cirrhotic patients^{12, 14}. The

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3 reduced coagulation ability, an increased vascular fragility and a large extension of sub-
4 mucosal oesophageal varices induced by the portal hypertension might explain the importance
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6 of bleeding from the post-banding induced ulcer without effective local thrombosis.
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10 The present study also stresses the importance of a local factor: the presence of peptic
11 oesophagitis as an independent predictive factor of this complication. These findings strongly
12 suggest that the mucosal damages induced by the acid exposure of the lower part of the
13 oesophagus might promote the early slippage of the rubber band or the bleeding from the
14 post-banding ulcer. When considering healing of post EVL ulcers, the use of PPI
15 (pantoprazole) has been reported to induce smaller lesions in comparison to placebo, but the
16 effect on bleeding was not conclusive^{15, 16}. In our study, all patients were treated with a mono
17 dose PPI during at least the first three days following EVL. Using higher doses of PPI might
18 have better prevented bleeding related to postbanding ulcer. Nevertheless there was no
19 difference regarding the use of extended PPI treatment (> 3 days) between cases and control
20 patient. Moreover it have been suggested that PPI therapy could be associated with a higher
21 risk of community-acquired pneumonia and spontaneous bacterial peritonitis in cirrhotic
22 patients^{17, 18}. Indeed, the acid gastric environment is considered an important barrier to
23 prevent colonization of the stomach and small intestine by ingested bacteria. Low-acid states
24 may compromise this barrier, increasing bacterial colonization and making the host more
25 susceptible to enteric infections and bacterial translocation¹⁹. Conversely, a recent meta-
26 analysis of clinical trials failed to show a conclusive association between PPI and respiratory
27 infection and a retrospective case control study including 116 cirrhotic patients did not find
28 any association between PPI use and spontaneous bacterial peritonitis^{20, 21}. The use of
29 sucralfate, known for its experimental mucosal cyto-protective action, has been proposed to
30 improve the ulcer healing following variceal sclerotherapy and ligation²²⁻²⁴. Compared to
31 antacid, sucralfate allowed a faster post EVL ulcer healing in a group of 45 randomized
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cirrhotic patients, but the association of both drugs was not assessed²⁵. In our study, we failed to find any benefit in the use of sucralfate for the prevention of bleeding related to post banding ulcer, but the number of treated patients was very low.

The independent predictive factors found would allow a better anticipation and prevention of the occurrence of post EVL ulcer bleedings. Alternatives to EVL should be evaluated in the prophylaxis of the bleeding induced by portal hypertension. The monitoring of beta-blockers using measurement of the hepatic venous pressure gradient has been reported to significantly reduce the risk of a first haemorrhage in patients with large varices and to improve survival^{26, 27}. In addition, two recent prospective, randomized studies have shown a long-term benefit and enhanced survival in hepatic venous pressure gradient-guided pharmacological treatment over EVL in cirrhotic patients for the prevention of rebleeding^{28, 29}. If confirmed, these data suggest that EVL might not be the first choice in the treatment of variceal bleeding, being reserved for emergency bleeding conditions or pharmacological nonresponders.

Finally several different endoscopic approaches have been proposed in order to substitute the EVL, clipping and detachable endoloops. In a preliminary study, variceal clipping has been shown to be effective in the management of bleeding oesophageal varices, without producing ulcer on attached site, as observed with band ligation, therefore avoiding the risk of haemorrhage³⁰. Similar observations have been reported with detachable endoloops, but without evaluation of the slippage of the snare and ulcer formation following the endoscopic treatment³¹.

In conclusion, the bleeding of ulcer due to spontaneous slippage of rubber band after EVL is a serious complication in which a fatal outcome seems to be influenced in the majority of cases by a sepsis. This present study pointed out at four independent predictive factors for the occurrence of this bleeding complication: presence of peptic oesophagitis, previous upper

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3 variceal digestive bleeding, a high APRI score and low prothrombin index. In patients with
4 these factors, a special care should be undertaken when an EVL is programmed in order to
5 minimize their importance and other treatment alternatives should be thought of. Further
6 prospective studies are necessary to confirm these results. Prevention of this complication is
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STATEMENT OF INTERESTS

Authors' declaration of personal interests: None

Declaration of funding interests: None

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FIGURE LEGENDS*Figure 1*

Receiver-Operator Characteristics (ROC) curve for prothrombin index (PI) to determine a threshold value allowing discrimination of patients with or without risk of developing bleeding related to post EVL ulcer.

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TABLES*Table 1 – Characteristics of patients*

Characteristics	"Cases" (n = 17)	Controls (n = 84)	p
Age (years)	54.6 (37-85)	58.5 (17-87)	.12
Male/Female	13/4 (76%/24%)	60/24 (71%/29%)	.77
Causes cirrhosis			
Alcohol	12(71%)	53(63%)	.78
Virus	3(18%)	27(32%)	.26
Others	5(29%)	13(15%)	.30
Child Pugh score	9.1 ± 2.6	7.7 ± 2.2	.02
Child Pugh Class			
A	2 (10%)	30 (36%)	.04
B	9 (53%)	32 (38%)	
C	7 (35%)	22 (26%)	
Previous Treatment			
β-blockers	4 (24%)	28 (33%)	.57
Aspirin/anticoagulation	1 (9%)	7 (8%)	1

Table 2 – Outcome of “cases” patients and mortality induced

	n (%)
Delay of occurrence (days)	13.5 ± 7.3 (range 2-29)
Mortality induced (in the 2 months)	11 (52)
Etiology of death	
Sepsis	5 (46)
Hepatic insufficiency	3 (27)
Uncontrolled bleeding	3 (27)

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Table 3 – Univariate analysis for history of the disease

History of disease	"Case" (n=17)	Control (n=84)	p
Ascites	8 (47%)	24 (28%)	.06
Spontaneous bacterial peritonitis	0 (0%)	1 (1%)	1.0
Hepatocellular carcinoma	1 (6%)	9 (11%)	1.0
History of upper variceal digestive bleeding	10 (59%)	27 (32%)	.02
Hepato renal syndrome	1 (6%)	1 (1%)	.32
Encephalopathy	1 (6%)	5 (6%)	1.0
Acute alcoholic hepatitis	2 (11%)	7 (8%)	.54

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Table 4 – Univariate analysis for biological tests

Blood analysis / score	"Case" (n=17)	Control (n=84)	p
Prothrombin index (%)	45.4± 14.1	56.1±13.7	.01
C reactive protein (mg/L)	17.6±18.3	11.7±16.3	.10
Albumin (g/L)	26.3±6.2	30.6±6.5	.02
ASAT/ALAT	2.2±0.9	1.9±1.0	.07
APRI score	3.5±3.4	20±1.7	.04
Bilirubin (micromol/L)	63.8±51.6	44.6±61.2	.04
Creatinine (micromol/L)	65.8±27.5	82.0±51.0	.05
Hemoglobin (mmol/L)	5.7±1.3	6.3±1.5	.26
Platelets (10 ⁹ /L)	98.3±47.1	101.4±52.3	.99

ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase

Score APRI = (AST (/ULN) x 100) / platelets (10⁹/L)

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Table 5 – Univariate analysis for endoscopic and haemorrhagic data

Endoscopic and haemorrhagic data	"Cases" (n=17)	Controls (n=84)	p
Peptic oesophagitis	5 (24%)	0 (0%)	.02
Indication of oesophageal variceal ligation			
Prophylactic	9 (53%)	50 (59%)	.038
Emergency	8 (47%)	34 (40%)	
Oesophageal varices grade II/III	4/15	32/52	.28
Gastric varices	4 (24%)	18 (21%)	1
Red signs	13(81%)	67 (80%)	.75
Dysphagia/post-EVL pain	0 (0%)	8 (10%)	.34
Number of rubber bands	5±1.8	5.3±2	.72
Antibioprophylaxis	11 (65%)	43 (51%)	.31
Use of Sucralfate	2 (12%)	20 (24 %)	.35
Use of proton pump inhibitors (> 3 days after EVL)	11 (65%)	50 (59%)	.69
Red cells transfusion (units)	1.7±2.3	1.2 ±1.8	.35
Plasma transfusion (units)	0.4±0.8	0.1±0.7	.01
Duration of Hospitalization	14.4±13.0	8.8±5.8	.09

Table 6 – Multivariate analysis

	Adjusted OR	CI 95 %	p
Age	1.06	.99-1.13	.12
Indication of oesophageal variceal ligation			
prophylactic	2.01	.51-7.88	.32
Emergency			
History of upper variceal digestive bleeding	12.07	2.30-63.43	.003
Ascites	3.04	.50-18.48	.23
Peptic oesophagitis	8.89	1.65-47.78	.011
APRI score	1.54	1.11-2.16	.011
Prothrombin index	.54	.31-.94	.031

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FIGURE

Figure 1

