Gut 1994; 35: 746–749

Bleeding peptic ulcer – risk factors for rebleeding and sequential changes in endoscopic findings

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Abstract

From September 1991 to December 1992, a prospective study was conducted to determine the risk factors and residual risk of rebleeding, and the evolutionary endoscopic changes in peptic ulcers that rebled. Emergency endoscopies were performed on 452 patients with haematemesis or a melaena, or both within 24 hours of admission. If the lesions were actively bleeding, then the patients were treated with injection sclerotherapy. A multivariate analysis of clinical, laboratory, and endoscopic variables of 204 patients with ulcer bleeding showed that hypovolaemic shock, a non-bleeding visible vessel, and an adherent clot on the ulcer base were independently significant in predicting rebleeding ($p<0.05$). Considering these three factors according to the estimates of their regression coefficients showed that a non-bleeding visible vessel was the strongest predictor of rebleeding. The study of the residual risk of rebleeding after admission showed that most rebleeding episodes (94·1%), including all associated with hypovolaemic shock, surgical treatment, and death, occurred within 96 hours of admission. After this time, the residual risk of rebleeding was less than 1%. Study of the changes in endoscopic findings before and after rebleeding illustrated that all ulcers with a visible vessel or adherent clot showed at follow up endoscopy were derived from ulcers with initial major stigmata. It is concluded that hypovolaemic shock, a non-bleeding visible vessel, and an adherent clot on an ulcer base are of independent significance in predicting rebleeding. Observation for 96 hours is sufficient to detect most rebleeding episodes after an initial bleed from peptic ulcer.

(*Gut* 1994; 35: 746–749)

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Accepted for publication
6 October 1993

Bleeding is a common, but serious complication of peptic ulcer disease. About 80–90% of bleeding episodes from peptic ulcers cease spontaneously.[1 2] For all these patients, the treatment course is comparatively uncomplicated and the death rate is 4% or less.[3 4] In patients with persistent or recurrent bleeding, however, the death rate can be as high as 30–40%, and emergent endoscopic or surgical intervention is usually required.[3 5] Although there are many published studies that discuss the endoscopic prediction of rebleeding in peptic ulcers,[6–9] most studies that evaluate the prognostic significance of a visible vessel have not taken into account the important clinical features that probably affect ulcer rebleeding, such as underlying medical illness and severity of bleeding.[10 11] In addition, there are no studies that evaluate risk factors for rebleeding by multivariate analysis of clinical, laboratory, and endoscopic parameters.

In clinical practice, determining the optimal stay in hospital for patients with bleeding ulcers is a crucial problem for physicians. A prolonged stay in hospital increases medical costs, while early discharge might result in an increase in preventable death of patients with severe rebleeding. Thus, the results of a study that evaluates the residual risk of rebleeding would possibly be helpful in this decision making.

We performed a prospective study to determine the risk factors and the residual risk for rebleeding peptic ulcer disease after the initial bleed. In addition, we investigated the sequential endoscopic changes of the ulcer from the time of the initial endoscopy to the time of rebleeding.

Patients and methods

PATIENTS

From September 1991 to December 1992, 452 consecutive patients with haematemesis or melaena, or both had emergency upper endoscopy performed within 24 hours of admission to our emergency unit. All patients with bleeding peptic ulcers proved by endoscopy who gave their consent were enrolled in the study. Criteria for exclusion included (a) the presence of other possible bleeding sites (for example, oesophageal varices, gastric cancer), (b) the presence of a systemic bleeding tendency (for example, decompensated liver cirrhosis, uraemia, use of an anticoagulant), (c) the intake of non-steroidal anti-inflammatory drugs within one week before admission, (d) alcoholism, or (e) the coexistence of an acute significant illness (for example, sepsis, stroke).

METHODS

Emergency endoscopies were performed within 24 hours of admission on all patients. The equipment used was the Olympus GIF XV10 and the GIF XQ 200. To improve the visual field, gastric lavage was carried out before endoscopy. The ulcers with stigmata were cleaned by water irrigation through the biopsy channel. Adherent clots were not removed with biopsy forceps. We divided the ulcer lesions into six categories according to a modified Wara's classification[12]: (a) bleeding visible vessel (either spurting or oozing), (b) non-bleeding visible vessel, (c) adherent clot, (e) oozing (without visible vessel), (f) red/black spot, and (g) clean

base. A non-bleeding visible vessel was defined as a raised red or bluish-red haemospheric lesion protruding from the ulcer base, without active bleeding. An adherent clot was defined as an overlying clot that was resistant to washing. A red or black spot was defined as a localised, small, red or black stigmata that was not protruding from the ulcer base. 'Active bleeding' was defined as the presence of either a 'bleeding visible vessel' or 'oozing' (without a visible vessel) from the ulcer base. All patients with active bleeding received endoscopic haemostatic treatment with local injection of epinephrine. To assess the significance of clinical and laboratory factors in predicting rebleeding, the following data were recorded for each patient: age, sex, past history of upper gastrointestinal bleeding, history of smoking, coexistence of an underlying medical disease (including diabetes mellites, hypertension, significant heart disease, chronic lung disease, compensated liver cirrhosis, and malignancy), initial blood pressure, initial pulse rate, presence of hypovolaemic shock before endoscopy, and serum blood urea nitrogen, creatinine, and alanine aminotransferase values on admission.

Patients who were haemodynamically stable on admission and had clean ulcer bases as shown by initial endoscopy, were discharged within 24 hours. Patients who had stigmata of bleeding were admitted for close observation and had follow up endoscopies every two days until the disappearance of the stigmata. During the stay in hospital, intravenous H_2 blockers were routinely given. The patients who developed rebleeding during the observation period were initially treated with therapeutic endoscopy, and were then given surgery if haemostasis could not be achieved. After discharge, patients received oral H_2 blockers and were followed up by telephone every other day. Patients were also requested to return to the outpatient clinic between day 3 and day 7 to check for evidence of rebleeding. The end points of this study were (a) death of the patient, or (b) observation for 10 days. 'Rebleeding' was defined as a subsequent ulcer bleeding episode that occurred after the initial bleed had stopped, as shown by follow up endoscopy or persistent haematemesis or melaena or both, with a change in vital signs. If medical treatment failed to achieve successful haemostasis, emergency surgery was performed.

STATISTICS

To determine the independent risk factors for rebleeding in patients who did not have actively bleeding ulcers at initial endoscopy, 16 clinical, laboratory, and endoscopic parameters of bleeding peptic ulcers were analysed by univariate analysis. A p value less than 0·05 was considered to be significant. Those parameters found to be significant by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify those that were independently significant in predicting rebleeding. In addition, estimates of regression coefficients were used to determine the risk of rebleeding. The residual risk of rebleeding was determined by calculating the resulting risk of rebleeding after a specific number of days had passed since admission.

Results

There were 239 patients with peptic ulcer bleeding initially enrolled in the study, with 12 patients dropping out during follow up. Table I shows the basic clinical data of the 227 patients. Stigmata of bleeding were present in the ulcers of 144 patients at initial endoscopy. Twenty three patients with active bleeding were treated by epinephrine local injection. Haemostasis was not achieved in two patients with bleeding visible vessels. They both subsequently had emergency surgery. The other ulcers with active bleeding were controlled at least temporarily with therapeutic endoscopy, with rebleeding occurring during the follow up period in four patients (19%). In three of the patients with severe rebleeding, haemostasis was not achieved by medical treatment and surgical intervention was required. The overall death rate in patients who presented with active bleeding at initial endoscopy was zero.

Two hundred and four patients presented without active bleeding and therefore were not treated with therapeutic endoscopy initially. During the follow up observation period, 17 of these patients rebled (8·3%). Endoscopic treatment failed to achieve haemostasis in five of them, and all five were sent for surgical treatment. Two patients died from surgical complications. The overall death rate in patients without initial active bleeding was 1·0%.

RISK FACTORS OF REBLEEDING

Univariate analysis of the 16 clinical, laboratory, and endoscopic variables in the 204 patients without active bleeding at initial endoscopy showed that seven were significantly associated with rebleeding: history of smoking, presentation with haematemesis, hypovolaemic shock before endoscopy, increased blood urea nitrogen, ulcer size larger than 1 cm, non-bleeding visible vessel, and adherent clot on the ulcer base (Table II). Multivariate analysis with stepwise logistic regression showed that only hypovolaemic shock, non-bleeding visible vessel, and adherent clot were independently significant in predicting rebleeding ($p<0·05$) (Table III).

TABLE I *Characteristics of patients*

Characteristics	*Patients (n=227)*
Age (y)	54 (17)*
Sex:	
Male	168 (74%)
Female	59 (26%)
Sites of ulcers:	
Gastric	84 (37%)
Duodenal	134 (59%)
Marginal	9 (4%)
Types of ulcers:	
Bleeding visible vessel	16 (7%)
Non-bleeding visible vessel	32 (14%)
Adherent clot	34 (15%)
Oozing	7 (3%)
Spots	55 (24%)
Clean	83 (37%)

*Mean (standard deviation).

TABLE II *Univariate analysis for rebleeding rate and principal parameters of bleeding peptic ulcers without active bleeding during initial endoscopy (n=204)*

Principal parameters	*Class*	*Rebleeding rate (%)*	*p Value*
Clinical factors:			
Age (y)	≥60	11/92 (12·0)	NS*
	<60	6/112 (5·4)	
Sex	Male	12/147 (8·2)	NS
	Female	5/57 (8·8)	
Past history of upper gastrointestinal bleeding	(+)	11/98 (11·5)	NS
	(−)	6/103 (5·8)	
Underlying disease†	(+)	3/26 (11·5)	NS
	(−)	14/167 (8·4)	
History of smoking	(+)	12/71 (16·9)	<0·01
	(−)	5/123 (4·1)	
Haematemesis	(+)	10/57 (17·5)	<0·05
	(−)	7/147 (4·8)	
Tachycardia	(+)	3/57 (5·3)	NS
	(−)	14/147 (9·5)	
Hypovolaemic shock	(+)	6/14 (42·7)	<0·05
	(−)	11/190 (5·8)	
Laboratory factors:			
Haemoglobin	<10	9/96 (9·4)	NS
	≥10	8/108 (7·4)	
BUN	>19 mg/dl	16/153 (10·5)	<0·05
	≤19 mg/dl	1/41 (2·4)	
Creatinine	>1·4 mg/dl	8/43 (18·6)	NS
	≤1·4 mg/dl	9/151 (6·0)	
ALT	>55 IU/l	3/21 (14·3)	NS
	≤55 IU/l	14/173 (8·1)	
Endoscopic factors:			
Site‡	Gastric	9/75 (12·0)	NS
	Duodenal	8/121 (6·6)	
Size	>1 cm	9/41 (22·0)	<0·05
	≤1 cm	9/163 (4·9)	
Number	1	8/71 (4·2)	NS
	>1	3/133 (10·5)	
Type	Non-bleeding visible vessel	14/32 (25·0)	<0·01
	Adherent clot	6/34 (17·7)	<0·05§
	Spot	2/55 (3·6)	NS§
	Clean base	2/83 (1·2)	

*NS denotes no significance; †underlying diseases indicate diabetes mellites, hypertension, significant heart disease, chronic lung disease, compensated liver cirrhosis, and malignancy; ‡marginal ulcer is not analysed secondary as too few cases; §for the comparison with the patient group with clean ulcer base.
BUN=blood urea nitogen; ALT=alanine aminotransferase.

RESIDUAL RISK OF REBLEEDING

Overall, rebleeding occurred in 21 of 225 patients whose ulcer bleeding had either stopped by the time of initial endoscopy (n=204) or had been stopped by endoscopic haemostastic treatment (n=21). In the group of 204 patients without initial active bleeding, 17 (8·3%) rebled. The time lapse between the initial stay in hospital and onset of rebleeding ranged from one to seven days. Most of the rebleeding episodes (94·1%) occurred within 96 hours after admission. Figure 1 shows the residual risks of rebleeding on each day after admission. In contrast, in the group of 21 patients with active bleeding at initial endoscopy, four (19%) rebled. All of these rebleeding episodes occurred within 96 hours after admission.

SEQUENTIAL CHANGES IN ENDOSCOPIC FINDINGS

Emergency endoscopy was performed for all rebleeding ulcers (n=21). In two cases it was too difficult to perform a detailed examination because bleeding obscured the visual field. Figure 2 shows the sequential changes of endoscopic findings after rebleeding in the other 19 patients. Analysis of the six categories of ulcers shows that they can be divided into two distinct groups. When an adherent clot, non-bleeding visible vessel or bleeding visible vessel was seen on initial endoscopy, one of these was always found on repeat endoscopy at the time of rebleeding. The same was found for the group of three remaining categories. When a red/black spot, oozing, or a clean base was found on initial endoscopy, one of these was always found on repeat endoscopy at the time of rebleeding (Fig 2).

The stigmata of the patients without rebleeding during the study period evolved with a general trend from adherent clots on initial endoscopy through non-bleeding visible vessels before becoming clean bases with an average duration of four days.

TABLE III *Stepwise logistic regression of risk factors for rebleeding*

Variable	*Estimate of regression coefficient*	*Standard error*	*p Value*
Hypovolaemic shock	1·655	0·7591	<0·05
Non-bleeding visible vessel	1·911	0·7561	<0·05
Adherent clot	1·721	0·8153	<0·05

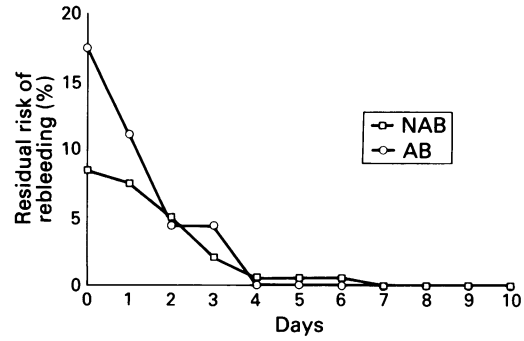

Figure 1: Analysis of residual risk of rebleeding of bleeding peptic ulcer each day after admission (NAB=patient group without active bleeding during initial endoscopy, AB=patient group with active bleeding and endoscopic haemostasis during initial endoscopy).

Discussion

In bleeding pepetic ulcers, recurrence, and persistence of bleeding are the most important factors that adversely affect prognosis, with their presence resulting in an up to 12-fold increase in death.[12] Several attempts have been made to identify endoscopic findings that are risk factors for rebleeding in pepetic ulcers.[6-9] There are no published works, however, which prospectively evaluate multiple clinical, laboratory, and endoscopic parameters by multivariate analysis, and which quantitatively assesses the risk factors for rebleeding. In this study, univariate analysis showed seven clinical and endoscopic risk factors that are associated with rebleeding, and multi-

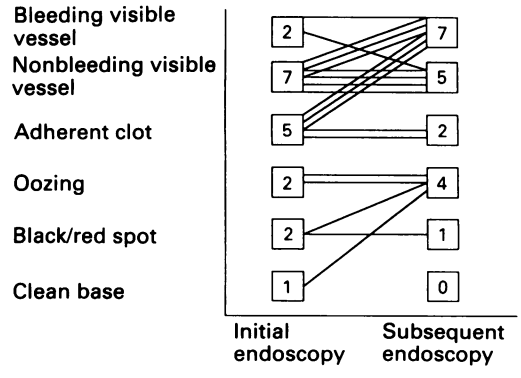

Figure 2: Changes in endoscopic appearance before and after rebleeding in 19 patients with bleeding peptic ulcers.

variate analysis with stepwise logistic regression reduced this number to three – that is, hypovolaemic shock, non-bleeding visible vessel, and adherent clot. When considering the three factors according to their estimates of regression coefficients, non-bleeding visible vessel on an ulcer base was the strongest factor in predicting rebleeding. It should be emphasised, however, that a combination of clinical and endoscopic factors may provide a more reliable prediction of rebleeding than individual criteria alone. We found that a non-bleeding visible vessel, associated with hypovolaemic shock had a 40% rebleeding rate, while a non-bleeding visible vessel without hypovolaemic shock had a rebleeding rate of only 25%. An adherent clot associated with hypovolaemic shock had a 50% rebleeding rate, but the presence of a clot without hypovolaemic shock had a rebleeding rate of only 17%. These findings are consistent with another prospective study, performed by Brearly *et al*,[13] which also showed the importance of hypovolaemic shock in predicting rebleeding.

The concept of residual risk of rebleeding in bleeding ulcers is quite important in determining appropriate patient management.[14] Both a prolonged stay in hospital and early discharge should be avoided. This study illustrates an important trend – most rebleeding episodes occur in the first 96 hours after admission. For example, Fig 1 illustrates that by 48 hours a patient without active bleeding on admission faces a residual risk of rebleeding of 4·9%; and the same patient faces a residual risk of rebleeding of less than 1% after 96 hours of observation. In addition, we found that all rebleeding episodes associated with hypovolaemic shock, the necessity of surgical intervention, or death or all three occurred within 96 hours. Therefore, we suggest that observation for 96 hours is sufficient for detecting most episodes of rebleeding. To establish, however, the optimal time for the stay in hospital for bleeding ulcer patients in a different population, a prospective study that considers the residual risk of rebleeding, severity of rebleeding and medical cost of a stay in hospital, is still needed.

The study of the sequential changes of endoscopic findings before and after rebleeding considers an important concept, which has been insufficiently studied in previous reports – all ulcers showing major stigmata (adherent clot, bleeding visible vessel and non-bleeding visible vessel) during or soon after rebleeding are derived from ones with major stigmata. In this study, none of the patients with a clean base, oozing, or spots on initial endoscopy showed a visible vessel or adherent clot during or soon after rebleeding. Based on these sequential endoscopic findings and the clinical course of rebleeding ulcers, it is therefore reasonable to divide bleeding peptic ulcers into two categories – one in which there is erosion of only capillaries or small sized vessels, and the other in which there is erosion of larger vessels. The first type results in oozing of ulcers and the formation of very small clots, – that is, red/black spots. The risk of rebleeding in this situation is quite low, but mild rebleeding might occasionally occur if the small clot drops off before completion of healing of the underlying tissue. In the second case, if an ulcer erodes a larger vessel, the bleeding is usually massive. Although an adherent clot might temporarily plug the bleeding hole during the haemostatic process, massive rebleeding often occurs if the clot drops off too early. By using a series of follow up endoscopies, we confirmed the natural sequential changes of stigmata of bleeding in peptic ulcers, as proposed by Johnston[10] – the healing process of stigmata progresses through the sequence of bleeding visible vessel, large red adherent clot, small white adherent clot, and ultimately disappearance of stigmata.

In conclusion, our study shows that: (1) the presence of hypovolaemic shock, a non-bleeding visible vessel, and an adherent clot are independent risk factors in predicting rebleeding in bleeding peptic ulcers; (2) the presence of a non-bleeding visible vessel is the most important factor in the prediction of rebleeding; (3) observation for 96 hours is sufficient to detect most rebleeding events; (4) all ulcers showing major stigmata during rebleeding are derived from ones with initial major stigmata.

The authors express their appreciation to Miss Su-Erb Lin for assisting case collection, to Drs Howard Dubner, Carl Berg, and Cheau-Jane Peng for revising the manuscript, and to Drs Ming-Juen Sheu and Pin-Wen Lin for their invaluable support for this study.

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