Original article

Active bleeding in benign gastro-duodenal ulcers: Predictors of failure of endoscopic injection hemostasis

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SUMMARY

The aim of this study was to define factors associated with failed endoscopic therapy in patients with active (spurting or oozing) upper gastrointestinal bleeding. We evaluated clinical and endoscopic parameters related to failure of injection hemostasis in 286 peptic ulcer patients with either active spurting or oozing bleeding. Endoscopic injection hemostasis was permanently successful in 218 (76.2%) and failed in 68 patients (23.8%) who needed surgical hemostasis. The overall mortality was 4.9 % (fourteen patients). In univariate analysis, therapeutic failure was significantly related to the presence of: 1) shock on admission (p<0,0001), hematemesis (p=012), spurting bleeding (p<0.001), low hemoglobin on admission (p=0,005), duodenal ulcers (p = 0.04), and stomal ulcers (p = 0.001). Previous peptic ulcer bleeding (p=0,013), or non-use of NSAID's (p=0,001) were negative predictors for the outcome of endoscopic hemostasis. In multivariate analysis, only shock, low hemoglobin concentration, non-use of NSAID's and spurting bleeding were negative predictors. It is possible, with specific characteristics, to define a subgroup of high-risk patients for continuing bleeding or rebleeding in spite of therapeutic endoscopy and, thus, candidates for complimentary endoscopic method of hemostasis or emergency surgical intervention.

Key words: endoscopic hemostasis, active bleeding, adrenaline injection, failure, peptic ulcer bleeding

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INTRODUCTION

Peptic ulcer disease represents the most common cause of acute non-variceal upper gastrointestinal hemorrhage, accounting for up to one half of all cases. Although peptic ulcer bleeding stops spontaneously in approximately 70-80% of patients, overall mortality still remains high.[1-4] Re-bleeding can occur in 10–30% of patients, and, without early treatment or surgical intervention, such patients are at high risk of death. In recent years, endoscopic injection therapy during emergency endoscopy has been proven, in randomized controlled trials, to reduce the need for emergency surgery in patients with active bleeding or non-bleeding visible vessel in the ulcer base.[5-9] However, a percentage of these patients, continues to bleed or re-bleed after injection therapy and many of them eventually require emergency surgical intervention. The presence of active bleeding (spurting or oozing) during emergency endoscopy has the greatest probability for either inadequate hemostasis or re-bleeding in spite of initial hemostasis. About 15-30% of these patients require emergency surgical hemostasis after endoscopic therapy.[10-12] The identification of this subgroup of patients may be of clinical importance because intensive monitoring and probably additional endoscopic treatments should be judged necessary. The aim of this study was to define factors associated with failed endoscopic injection therapy in a large series of patients with active spurting or oozing bleeding peptic ulcers during emergency endoscopy.

PATIENTS AND METHODS

From January 1999 to December 2002, 1113 patients were admitted to our hospital due to peptic ulcer bleeding

or who bled during hospitalisation for other reason. Patients underwent emergency endoscopy performed, either during the first 24 hours after admission or immediately after resuscitation, in patients with massive bleeding. Endoscopic injection hemostasis with adrenaline diluted 1:10.000 in saline 0.9% (A/S) was performed on all patients with active spurting or oozing bleeding or a non-bleeding visible vessel (NBVV) during emergency endoscopy. Endoscopic A/S injections were performed with a flexible, one-use injector, passed through the working channel of the endoscope, into the ulcer base in a circumferential fashion, as close to the visible vessel as possible. About 15 ml were routinely injected and up to 30 ml in difficult hemostases.

After endoscopic hemostasis, patients were carefully observed and managed by the same medical team of gastroenterologists and surgeons. Blood pressure and pulse rate were checked before endoscopy and after injection therapy. All patients with peptic ulcer bleeding routinely received proton pump inhibitors in standard doses (*40mg omeprazole IV/. day)* Blood transfusion was given if hemoglobulin (Hb) was less than 10 g/dl.

Active bleeding during emergency endoscopy was characterized as spurting or oozing according to Forrests' classification.[13] We studied only patients with active spurting or oozing bleeding during the emergency endoscoppy. Patients with a non-bleeding visible vessel were not included in this study. No exclusion was made on the basis of age or coexisting diseases. A recurrence of bleeding was defined by the vomiting of fresh blood, melena, or both, combined with either shock or decrease in the hemoglobin concentration by at least 2 g /dl over a 24 – hour period, if occurring after the early stabilization of blood pressure, pulse, and the hemoglobin concentration. In case of re-bleeding, endoscopy was repeated, and in some patients a second endoscopic hemostasis or endosclips was carried out. The second endoscopic hemostasis with injection and/or setting of endosclips when technically possible and if the bleeding is severe, has been routinely performed in our hospital in the last two years. Patients were submitted to emergency surgical hemostasis if there was: a) no improvement despite transfusion of more than 5 units in 24 hours or 12 units in 48 hours and b) rebleeding in hospital with hemodynamic evidence of shock (systolic pressure <100mmHg, pulse rate>100/ min).

Patients who failed to achieve permanent hemostasis and required emergency surgery were considered as endoscopic failures. A large number of clinical and endoscopic factors were compared with those patients who achieved permanent hemostasis. We evaluated the following variables: patient age, sex, smoking, alcohol, previous non-steroidal anti-inflammatory drug (NSAID's) consumption, the presence of hypovolemic schock, hematemesis, coexisting diseases, hemoglobulin at admission, ulcer localisation, peptic ulcer history or peptic ulcer bleeding history.

All these parameters were correlated with the need for surgical intervention initially by using univariate analysis. Continuous variables were expressed as mean ± SD (standard deviation) and were compared, using Students't test. Categorical variables were expressed as percentages and were compared using, X^2 test. Variables found to be significant in the univariate analysis ($p<0.05$) were included in a multivariate stepwise logistic regression model. Statistical analysis was performed using SPSS version 10.0 for Windows.

RESULTS

Endoscopic injection therapy was performed on 286 patients with active bleeding (231 men and 55 women) with a median age of 58.2 ± 17.2 years (Table 1). The active bleeding was characterized as spurting in 120 patients and oozing in 166 patients. Initial hemostasis was achieved in 252 of the 286 patients (88.1%). In 12 patients the attempt of hemostasis failed because of massive bleeding or difficult ulcer localization. Two patients underwent a second successful attempt over the next 12 hours. There was no remarkable change in the blood pressure or pulse rate in patients who underwent

Table 1. Details of patients recruited to the study

	N = 286	
Mean age in years (± SD)	57.8 ± 17	
Men/Women	231/55	
Duodenal ulcers (%)	179	(62,6 %)
Gastric ulcers (%)	86	(30 %)
Stomal ulcers (%)	21	(7.4 %)
Ulcerogenic drugs consumption (%)	152/186	(53.1%)
Active spurting (Forrest 1a)	120/286	
Active oozing (Forrest 1b)	166/286	
Hemoglobulin at admission (gr/100 ml) ± SD	9.9 ±2.4	
Emergency surgery (%)	68/286	(23.8 %)
Mortality	14/286	(4.9%)
Postsurgical mortality	9/68	(13.2 %)

SD: standard deviation

injection therapy. No patient developed cardiac arrythmias, or uncontrollable bleeding due to hemostasis. Eighteen patients underwent a second endoscopic hemostasis with injection of A/S (8 patients) or endoclips (10 patients) because of re-bleeding, while, in the other patients with re-bleeding, no second endoscopic injection therapy or any other hemostatic method was performed. From the group of patients with second hemostasis, permanent cessation of bleeding was achieved in 11 patients (4 patients with injection and 6 with injection/ and endosclips). In general, endoscopic hemostasis was permanently successful in 218 patients (76.2%). Emergency surgical hemostasis for persistent or recurrent bleeding was required in 68 patients (23.8%). Fourteen patients died (4.9%), nine of them after surgery (9/68 with a post-surgical mortality rate of 13.2 %). Causes of death were respiratory failure (n = 6, two of them preoperatively), cerebral ischemia (n = 3, one of them pre-operatively), hemorrhagic shock (n=1, the patient died pre-operatively), cardiovascular failure (n=2, one of them pre-operatively) and pulmonary embolism (n=2, the patients died post-operatively).

In univariate analysis, therapeutic failure was significantly related to the presence of shock on admission (p<0.0001), hematemesis (p=0.012), spurting bleeding (p<0.0001), and stomal ulcers (p=0.001) at emergency endoscopy (Table 2). Endoscopic injection therapy was significantly less effective in patients with chronic ulcers compared to those who had acute NSAID's related ulcers. Previous peptic ulcer bleeding (p=0.013), or non-use of NSAID's (p=0.001) were negative predictors for the outcome of endoscopic hemostasis. Patients in whom the therapy failed had less hemoglobulin concentration at admission (8.4 ±1.9 gr/ dl vs 10.4 ±2.5 gr/dl), p < 0.005.

In multivariate analysis shock (p=0.0012) and low hemoglobulin concentration (p=0.005) at admission, as well as non-use of non NSAIDs (p=0.04) and spurting bleeding at emergency endoscopy (p<0.0001), were negative predictors (Table 3).

DISCUSSION

Endoscopic hemostasis is widely used to control bleeding in patients with active peptic ulcer bleeding or NBVV in the ulcer base. According to many published reports, endoscopic treatment (including heater probe, bipolar electrocoagulation, laser and injection therapy) significantly reduces the rates of further bleeding and the need for blood transfusion, hospital costs and emergency surgery.[5-6,14-16] These endoscopic therapeutic methods are comparable in their safety and efficacy. Although there is no agreement on which is the best endoscopic hemostatic method, many endoscopists prefer injection of adrenaline solution, because of its simplicity, safety and effectiveness as the first line treatment for peptic ulcer bleeding.[10-12,17-19]

Although endoscopic therapy in patients with ulcers with active bleeding reduces rebleeding and emergency

Table 2. Clinical and endoscopic factors related to failure of endoscopic injection therapy in univariate analysis.

	Permanent hemostasis N=218	Hemostasis failure N=68	P
Age	58.6 ± 16.9	57.3 ± 18	Ns
Male sex	169	62	0.013
Peptic ulcer history	69	28	NS
Peptic ulcer bleeding history	76	35	0.013
NSAIDs use	128	24	0.001
Smoking	91	30	NS
Alcohol abuse	24	8	NS
Coexisting diseases	99	31	NS
Presence of shock	17	23	<0.001
Hematemesis	72	34	0.012
Hemoglobulin at admission (gr/dl)	10.4 ±2.5 l	8.4±1.9	0.005
Duodenal ulcer	144	35	0.022
Gastric ulcer	66	20	NS
Stomal ulcer	8	13	0.001
Spurting bleeding	57	63	<0.001

Table 3. Clinical and endoscopic factors related to failure of endoscopic injection therapy in multivariate analysis

	Permanent hemostasis N=218	Hemostasis failure N=68	P
NSAID's use	128	24	0.04
Presence of shock	17	23	0.0012
Spurting bleeding	57	63	<0.001
Hemoglobulin at admission gr/dl	10.4 ±2.5 1	8.4 ±1.9	0.005

surgery, about 10-30% of patients require emergency surgery for permanent hemostasis.[8,20] In our study, performing endoscopic injection of diluted adrenaline, 23.8% of patients with active (spurting or oozing) bleeding underwent emergency surgical hemostasis. Hemostasis failure was mainly in active spurting (52.5%), while in patients with active oozing, endoscopic failure was very rare (3%). These patients usually had a large vessel on the ulcer base and experimental studies have shown that local treatment is not effective in ulcers with arteries greater than 1mm in diameter.[21] Also high volume active bleeding prevents endoscopist from visualling the lesion, or injecting adequate material. However, the benefit of further endoscopic treatment, or a second look endoscopy is still controversial. The identification of a high risk group of patients for further bleeding, by using clinical and endoscopic factors, would be useful in the monitoring, and treatment of these patients.[20-29]

Among clinical risk factors, the presence of hypovolemic shock on admission was significantly more common among those who failed endoscopic therapy. This is not surprising since this group of patients had the worst prognosis without endoscopic treatment.[30-31] Hematemesis, as a clinical feature of bleeding, was not associated with increased risk of failure. Although age and concomitant diseases are the major factors which affect mortality in peptic ulcer bleeding patients[2-4] it did not predict the outcome of endoscopic therapy, probably because endoscopic injection of adrenaline is an easily performed hemostatic method and no complications have been reported so far. Choudari and colleagues, performing endoscopic hemostasis in a large group of unselected patients with major peptic ulcer bleeding, found no difference in the outcome of patients in different age groups [less than 60 years, 61-74 years and over 75 years old].[31]

Also, in this study active bleeding chronic ulcers found to be more prone to hemostasis failure than acute NSAID related ulcers. Although NSAID's affect platelet function and the median age is greater in this group of patients, this variation may be due to differences in bleeding vessels and/or difficulties in performing endoscopic therapy. Acute ulcers usually erode submucosal vessels whereas, chronic duodenal ulcers may erode deeper and larger serosal vessels which rarely respond to any form of local therapy.[32] Moreover, chronic duodenal ulcers produce destruction of the duodenal bulb, which, especially in cases with active spurting bleeding, makes endoscopic injection therapy difficult or even impossible. On the other hand, endoscopic injection hemostasis is easier in a normal duodenal bulb or stomach, even with an ulcer high in the lesser curvature. Bleeding gastric ulcers have been more accessible to hemostasis (99%) than bleeding duodenal ulcers (88-92%) in previous studies.[33-35]

In conclusion, it is possible to define specific clinical and endoscopic variables related to rebleeding, in spite of therapeutic injection hemostasis in patients with active bleeding ulcers. The identification of this sub-group during emergency endoscopy could protect them from recurrent bleeding, transfusion of large volumes of blood by applying intensive monitoring, and timely correct surgical hemostasis or, possibly, another complementary endoscopic hemostatic method.

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