Factors related to the failure of endoscopic injection therapy for bleeding gastric ulcer

E Brullet, R Campo, X Calvet, D Coroleu, E Rivero, J Simó Deu

Abstract

***Background*—Although endoscopic injection therapy is effective in controlling initial haemorrhage from peptic ulcer, between 10% to 30% of patients suffer rebleeding.**

***Aim*—To assess the factors that may predict the failure of endoscopic injection in patients bleeding from high risk gastric ulcer.**

***Subjects*—One hundred and seventy eight patients admitted for a gastric ulcer with a bleeding or a non-bleeding visible vessel were included.**

***Methods*—Patients received endoscopic therapy by injection for adrenaline and polidocanol. Twelve clinical and endoscopic variables were entered into a multivariate logistic regression model to ascertain their significance as predictive factor of therapeutic failure.**

***Results*—Eighty seven per cent (155 of 178) of patients had no further bleeding after endoscopic therapy. Endoscopic injection failed in 23 (13%) patients: 20 (12%) continued to bleed or rebleed, and three (1%) patients could not be treated because of inaccessibility of the lesion. Logistic regression analysis showed that therapeutic failure was significantly related to: (1) the presence of hypovolaemic shock (p=0·09, OR 2·38, 95% CI: 0·86, 6·56), (2) the presence of active bleeding at endoscopy (p=0·02, OR 2·98, 95% CI: 1·12, 7·91), (3) ulcer location high on the lesser curvature (p=0·04, OR 2·79, 95% CI: 1·01, 7·69), and (4) ulcer size larger than 2 cm (p=0·01, OR 3·64, 95% CI: 1·34, 9·89).**

***Conclusion*—These variables may enable identification of those patients bleeding from gastric ulcer who would not benefit from injection therapy.**

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Keywords: bleeding peptic ulcer, endoscopic injection, upper gastrointestinal bleeding, gastric bleeding, rebleeding, therapeutic endoscopy.

Consorci Hospitalari Parc Taulí, Sabadell, Barcelona, Spain
E Brullet
R Campo
X Calvet
D Coroleu
E Rivero
J Simó Deu

Correspondence to:
Dr E Brullet, Endoscopy Unit, Consorci Hospitalari Parc Taulí, Parc Tauli sn, 08208 Sabadell, Spain.

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Endoscopic injection therapy (EIT) is a cost effective and safe method in treating bleeding from peptic ulcer.[1] However, between 10% to 30% of patients continue to bleed or rebleed after EIT. The identification of the subgroup of patients unlikely to benefit from endoscopic injection may be of clinical importance to offer other alternative treatments without delay.[1–3]

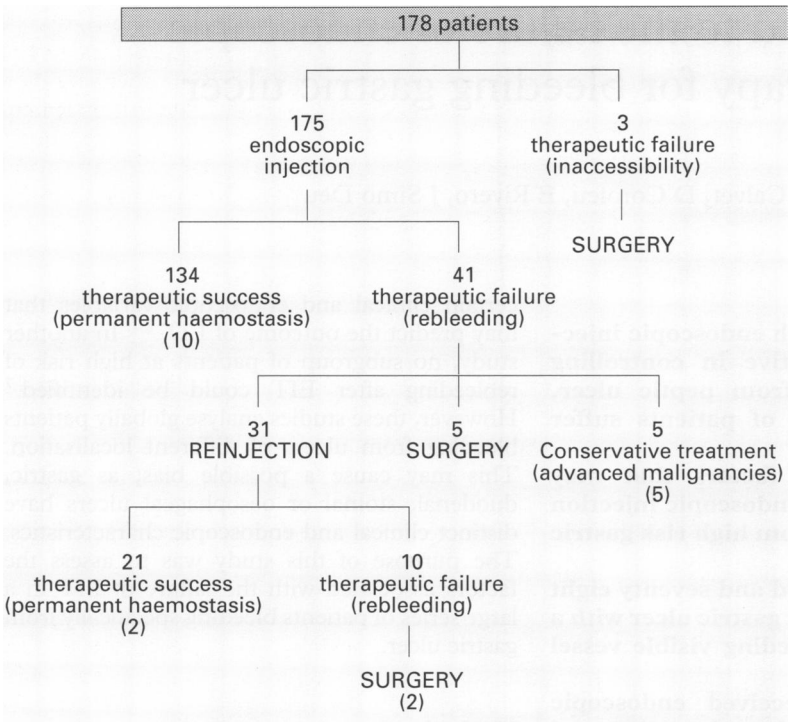
Only a few studies have focused on the assessment of the factors that may be associated with EIT failure. Two of these studies have identified certain clinical and endoscopic variables that may predict the outcome of EIT.[4–6] In another study, no subgroup of patients at high risk of rebleeding after EIT could be identified.[7] However, these studies analyse globally patients bleeding from ulcers of different localisation. This may cause a possible bias; as gastric, duodenal, stomal or oesophageal ulcers have distinct clinical and endoscopic characteristics. The purpose of this study was to assess the factors associated with the failure of EIT in a large series of patients bleeding specifically from gastric ulcer.

Methods

Patients

From January 1990 to December 1993, 1661 patients were admitted with upper gastrointestinal bleeding or developed it during hospitalisation for unrelated disorders. All patients underwent emergency endoscopy within 12 hours of admission. A gastric ulcer with a bleeding (oozing or spurting) or a non-bleeding visible vessel was found in 178 patients. The ulcer floor was routinely irrigated by jets of water to remove debris or blood clots. A visible vessel was defined as a red or black mound-like elevation through the ulcer floor resistant to gentle washing.[8] Endoscopic therapy was carried out during emergency endoscopy by injection of 8–15 ml of adrenaline (1/10 000) followed by injection of 3–10 ml of polidocanol (1%), in measures of 0·5–1 ml around and into the vessel.

Endoscopic characteristics of gastric ulcers were prospectively recorded. The lesions were classified according to: (a) the endoscopic stigmata (spurting, oozing, non-bleeding), (b) the size measured by means of an open biopsy forceps and classified as larger or smaller than 2 cm, and (c) the anatomical location defined as: high (ulcers located less than 10 cm from the cardia), middle, and pyloric (ulcers located less than 5 cm from the pylorus).[9] The severity of the haemorrhage was assessed by the presence or absence of hypovolaemic shock. Hypovolaemic shock was defined as the presence of a systolic blood pressure less than 100 mm Hg and peripheral circulatory failure, or the presence of compensated shock, with postural hypotension defined as a fall of more than 20 mm Hg sitting in an upright position, associated with peripheral circulatory failure. Clinical status of patients was evaluated according to the ASA classification[10]: ASA I=healthy patient, ASA II=patient with mild systemic disease without functional limitations, ASA III=severe systemic disease with definite functional



Outcome of patients.

limitation, ASA IV=severe systemic disease that is a constant threat to life, and ASA V= moribund patient not expected to survive 24 hours with or without operation.

After EIT, the gastric content was monitored by hourly observation of the nasogastric aspirate and all patients were given ranitidine (initially 50 mg intravenously six hourly, and after oral intake, 150 mg orally twice a day).

Patients in whom definitive haemostasis was achieved after one or two sessions of EIT were considered as endoscopic treatment successes. Patients who presented persistent or recurrent bleeding after EIT, or in whom EIT could not be performed because of inaccessibility were considered as therapeutic failures. Persistence of haemorrhage was defined as the non-cessation of bleeding immediately after EIT or as the presence of haematemesis or fresh blood from the nasogastric aspirate accompanied by a decrease of systolic blood pressure greater than 15 mm Hg within the initial six hours after endoscopic injection. Recurrent bleeding was defined as the occurrence of these conditions after this period of six hours or if more than four units of packed red cells had to be infused during the first 48 hours to maintain a minimum haemoglobin value of 10 g/dl after haemodynamic stabilisation.

Patients with persistent haemorrhage after EIT were submitted to emergency surgery. Patients with recurrent bleeding were treated individually (reinjection or surgery) in accordance with associated diseases and surgical risk. Emergency surgery was indicated in the patients for whom EIT could not be applied.

The following variables from both clinical and endoscopic reports were analysed: age, sex, previous history of non-steroidal anti-inflammatory drugs (NSAID) use, physical status (measured by the ASA classification), presence of hypovolaemic shock, transfusional requirements (number of units of red blood cells), haemoglobin concentration, anatomical location and size of the ulcer, endoscopic stigmata, and amount of adrenaline and polidocanol injected.

Statistics

Univariate analysis was performed for each variable to ascertain their significance as predictive factor of EIT failure using the Pearson χ^2 test for categorical and ordinal variables, and *t* test for continuous variables. Significant predictive factors ($p<=0{\cdot}25$) were entered into a multivariate logistic regression model and examined for significance of the likelihood ratio using a stepwise procedure with backward elimination. Goodness of fit of the final model was assessed using the Hosmer-Lemeshow χ^2 test.[11] The area under the receiver operating characteristic (ROC) curve, as a measure of the discrimination of the model, was calculated. Data analysis was performed using the SPSS/Windows statistical Package.

Results

One hundred and seventy eight patients fulfilled the criteria necessary for EIT (Figure). Three patients could not be treated because of the inaccessibility of the lesion and underwent emergency surgery.

EIT was performed in 175 patients. Permanent haemostasis was achieved in 134 of 175 patients treated. Forty one patients had further bleeding after EIT. In this group of treatment failures, five patients were treated with conservative measures because of their preterminal status, five patients underwent emergency surgery, and a second session of endoscopic injection was carried out on 31 patients. Twenty one of these 31 reinjected patients had no further bleeding, while the other 10 patients underwent surgical operation because of repeated therapeutic failure.

Overall success rate of EIT was 87% (155 of 178). The rebleeding rate after first EIT was 23·4% (41 of 175 patients treated), and 32·2% (10 of 31 patients reinjected), Thus the overall rebleeding rate of EIT was 12% (23 of 175 treated patients).

Only one complication resulted from EIT: gastric wall necrosis set in 15 days after injection with fatal outcome.

The overall death rate was 10·6% (19 of 178), 7·7% (12 of 155) in those patients in whom definitive haemostasis was achieved after EIT, and 30·4% (seven of 23) in the group of patients in whom EIT failed (Figure). Death rate for surgically operated patients was 11% (two of 18 operated patients).

Table I shows the univariate analysis of clinical and endoscopic variables. Logistic regression was used to adjust simultaneously for multiple covariates. The final model showed that the presence of hypovolaemic shock ($p=0{\cdot}09$, OR 2·38, 95% CI: 0·86, 6·56),

TABLE I *Univariate analysis: factors related to the outcome of endoscopic injection*

	Endoscopic injection		
	Success	*Failure*	*p Value*
Age*	64·69 (15·5)	67·07 (14·34)	0·46
Sex			
Male	103 (85)	18(15)	0·25
Female	52 (91)	5 (9)	
ASA category			
I, II	91 (90)	10 (10)	0·16
III, IV, V	64 (83)	13 (17)	
NSAID use			
Absent	81 (92)	7 (8)	
Present	74 (82)	16 (18)	0·05
Shock			
Absent	126 (90·5)	13 (9·5)	
Present	29 (74·5)	10 (25·5)	0·007
Haemoglobin (g/dl)*	9·29 (2·01)	8·74 (2·31)	0·23
Endoscopic stigmata			
Active bleeding	37 (74)	13 (26)	0·004
Non-bleeding	118 (92)	10 (8)	
Ulcer location			
High	54 (77)	16 (23)	0·005
Medium and pyloric	101 (93·5)	7 (6·5)	
Ulcer size			
<2 cm	104 (94)	7 (6)	
>2 cm	51 (76)	16 (24)	0·0007
Volume injected (ml)*			
Adrenaline	9·8 (1·8)	12·5 (2·4)	0·20
Polidocanol	5·7 (2·2)	7·4 (2·5)	0·10
Patients transfused within the 48 hours after injection:			
≤2 RBC units†	81 (98·7)	1 (1·2)	0·0001
>3 RBC units	74 (77)	22 (33)	

*Continuous variables are expressed as mean (SD). Other values in parentheses are percentages.
†RBC=red blood cells.

TABLE II *Rebleeding rate after EIT in patients bleeding from gastric ulcer in different studies*

Author (reference)	*Patients included with gastric ulcer (n)*	*Rebleeding rate (%)*	*Agent used*
Villanueva[4]	111	21	ADRE+POLC
Saeed[5]	31	3	Ethanol
Choudari[7]	120	20	ADRE or HPT
Hirao[17]	114	5	HS+ADRE
Sugawa[18]	17	13	Ethanol
Brullet[19]	55	15	ADRE+POLC
This study	175	13	ADRE+POLC

Abbreviations: HS=hypertonic saline, ADRE=adrenaline, PODL=polidocanol, HPT=heater probe thermocoagulation.

the presence of active bleeding (p=0·02, OR 2·98, 95% CI: 1·12,7·91), location high on the lesser gastric curvature (p=0·04, OR 2·79, 95% CI: 1·01, 7·69), and ulcer size larger than 2 cm (p=0·01, OR 3·64, 95% CI: 1·34, 9·89) were the variables significantly associated with the failure of endoscopic therapy. The ROC curve showed an excellent discrimination (80·6%) of the model.

The ulcer size was the strongest predictive factor of EIT failure. Patients bleeding from gastric ulcers larger than 2 cm had a 3·6 times higher risk for rebleeding. The presence of hypovolaemic shock failed to achieve normal significance (p=0·09), but none the less seemed to be an important predictor of further bleeding after EIT. The inclusion of this variable improved the goodness of fit of the model as well as its discrimination.

Discussion

Despite the fact that endoscopic injection is effective in controlling initial haemorrhage from peptic ulcer, between 10% and 30% of patients suffer rebleeding.[12–16] No consensus exists about what should be done when EIT fails, and it is still controversial if a further endoscopic attempt is of benefit or it may delay surgical operation.[2 3] Thus identification of those factors predisposing to the failure of EIT would be of clinical relevance in selecting those patients unlikely to benefit from this treatment.

This study was restricted to a group of patients bleeding from high risk gastric ulcer. Permanent haemostasis was obtained in 87% of cases, that is within the range of published results[4–7 17–20] (Table II). Rebleeding occurred in 12% of cases, and in only a few patients (1%) EIT could not be applied because of inaccessibility to the bleeding point. Multivariate logistic regression analysis showed that the presence of hypovolaemic shock, active bleeding at endoscopy, ulcer location high on the lesser gastric curvature, and ulcer size larger than 2 cm were the variables significantly related to EIT failure.

Among the clinical factors analysed, only the presence of hypovolaemic shock was significantly related to the EIT outcome. Its presence increased 2·8 times the risk of EIT failure. Although its p value was 0·09, the presence of shock has clinical significance because it indicates the amount of blood loss, and thus its inclusion improves the goodness of fit of the model as well as a better discrimination between patients in whom permanent haemostasis was achieved and those who rebleed. As in other studies,[7 20–24] the presence of active bleeding was also related to EIT failure, increasing the risk of further bleeding by 2·9 times. The relation between failure of EIT in those patients who presented with active bleeding or hypovolaemic shock may show that these patients had a large vessel on the ulcer base.[1–3] In this sense, experimental studies have shown that local treatments are not effective in ulcers with arterial breaches greater than 1 mm in diameter.[25–28] Moreover, active haemorrhage may make reaching the bleeding point difficult, preventing adequate injection or even, making it impossible. In this sense, several authors recommend the use of thermal methods in actively bleeding ulcers.[3 21–25]

Other clinical factors proposed as predictors of endoscopic treatment failure such as age, NSAID use, concomitant diseases, number of transfusions or haemoglobin concentration[1 4 5 7 20 21] did not reach statistical significance in multivariate analysis. Among these factors, the presence of severe associated diseases is of particular interest as it was found that it did not influence the therapeutic outcome. Similar findings have been reported by Choudari *et al*[7] and Chen *et al*,[21] and they state that patients with multisystemic associated diseases are probably at high risk of dying in hospital, but their haemostatic response to EIT is no different to those without them. In contrast, other authors[4–6] have found that the existence of concomitant diseases is a primary determinant of rebleeding after EIT. Methodological differences because of the inclusion of different types of ulcers (gastric, duodenal, stomal, and oesophageal) may almost partially explain these discrepancies. Moreover, the poor response to EIT seen in these studies may also be related to other

concomitant factors rather than to the presence of severe associated diseases. In this sense, Villanueva *et al*[4] found a high proportion of larger size ulcers in those patients with severe associated disorders.

Concerning the two other endoscopic factors, EIT was significantly less effective in patients having ulcers larger of 2 cm and located high in lesser gastric curvature. Similar findings have previously been reported by us[19] and other authors.[4–7 9 21 27 29 30] In this study, the ulcer size was the variable that was most significantly related to therapeutic failure, increasing it 3·64-fold. This may be partially related to technical difficulties of access to large ulcers with large vessels deeply located in the gastric wall, resulting in failure to apply adequate injection. In this sense, we have also found that the ulcer size is the main predicting factor of EIT failure in another study that included a large series of patients bleeding specifically from duodenal ulcer.[31] Similar findings have also been reported by Villanueva *et al*.[4] In contrast, the ulcer size is not considered in Baylor's score,[5 6] while it was not formally measured in the study of Choudari *et al*.[7] Concerning ulcer position, it has previously been reported that ulcers located high on the lesser gastric curve rebleed more frequently.[9 19 23] In this study, this variable increased the risk of EIT failure 2·79-fold compared with medium or prepyloric ulcers. This feature may be related to both the close anatomical relation between this location and the left gastric artery or its branches, as well as to technical reasons, specially in those ulcers only accessible to injection under retroflexion.

The findings of this study lead us to conclude that EIT is useful in treating bleeding from high risk gastric ulcer as permanent haemostasis is obtained in 87% of cases. The problem of accessibility (1%) seems to be less relevant than in duodenal ulcer (8–12%).[2 14 31] Patients presenting with hypovolaemic shock and having large ulcers, located high on the lesser gastric curvature or with an actively bleeding vessel have high risk of rebleeding after EIT. Intensive monitoring and additional treatments such as thermal endoscopic methods or early surgery should be considered for this group of patients.[1–3] Future perspectives such as transcatheter arterial embolisation need further evaluation.[32] Doppler ultrasound study of the involved vessel might contribute in identifying the ulcers at true risk of endoscopic injection failure.[33]

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