

Predictors of rebleeding after initial hemostasis with epinephrine injection in high-risk ulcers

Ming-Luen Hu, Keng-Liang Wu, King-Wah Chiu, Yi-Chun Chiu, Yeh-Pin Chou, Wei-Chen Tai, Tsung-Hui Hu, Shue-Shian Chiou, Seng-Kee Chuah

Ming-Luen Hu, Keng-Liang Wu, King-Wah Chiu, Yi-Chun Chiu, Yeh-Pin Chou, Wei-Chen Tai, Tsung-Hui Hu, Shue-Shian Chiou, Seng-Kee Chuah, Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Niao-Song Hsiang 833, Kaohsiung, Taiwan

Author contributions: Chuah SK designed the research; Hu ML performed the research and wrote the paper; Tai WC, Chiu YC, Chou YP, Hu TH and Chiou SS contributed equally to this work; Wu KL and Chiu KW and Chuah SK performed critical revision.

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Correspondence to: Dr. Seng-Kee Chuah, Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, 123, Ta-Pei Road, Niao-Song Hsiang 833, Kaohsiung, Taiwan. chuahsk@seed.net.tw

Telephone: +886-7-7317123 Fax: +886-7-7322402

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Abstract

AIM: To identify the predictors of rebleeding after initial hemostasis with epinephrine injection (EI) in patients with high-risk ulcers.

METHODS: Recent studies have revealed that endoscopic thermocoagulation, or clips alone or combined with EI are superior to EI alone to arrest ulcer bleeding. However, the reality is that EI monotherapy is still common in clinical practice. From October 2006 to April 2008, high-risk ulcer patients in whom hemorrhage was stopped after EI monotherapy were studied using clinical, laboratory and endoscopic variables. The patients were divided into 2 groups: sustained hemostasis and rebleeding.

RESULTS: A total of 175 patients (144, sustained

hemostasis; 31, rebleeding) were enrolled. Univariate analysis revealed that older age (≥ 60 years), advanced American Society of Anesthesiology (ASA) status (category III, IV and V), shock, severe anemia (hemoglobin < 80 g/L), EI dose ≥ 12 mL and severe bleeding signs (SBS) including hematemesis or hematochezia were the factors which predicted rebleeding. However, only older age, severe anemia, high EI dose and SBS were independent predictors. Among 31 rebleeding patients, 10 (32.2%) underwent surgical hemostasis, 15 (48.4%) suffered from delayed hemostasis causing major complications and 13 (41.9%) died of these complications.

CONCLUSION: Endoscopic EI monotherapy in patients with high-risk ulcers should be avoided. Initial hemostasis with thermocoagulation, clips or additional hemostasis after EI is mandatory for such patients to ensure better hemostatic status and to prevent subsequent rebleeding, surgery, morbidity and mortality.

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Key words: Epinephrine injection; High-risk ulcers; Initial hemostasis; Predictors; Rebleeding

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INTRODUCTION

Bleeding peptic ulcer is a common and life-threatening

medical emergency^[1]. With regard to endoscopic hemostasis, epinephrine injection (EI) monotherapy is a common and effective endoscopic method of hemostasis because of its low risk, low cost and high accessibility^[2-4]. Although EI monotherapy has good efficacy in the hemostasis of bleeding peptic ulcers, bleeding recurs in about 10%-30% of the population^[5-8]. Undoubtedly, recurrent bleeding remains the most important adverse independent prognostic factor^[9,10]. Recent studies have revealed that thermocoagulation, sclerosant injection or clips alone, or combined with EI are superior to EI alone for preventing rebleeding, surgery and mortality. EI alone is not recommended^[11-15]. However, the reality is that EI monotherapy to arrest ulcer bleeding is still commonly practiced, in part, because it is a relatively simple and effective hemostatic method and because some patients are intolerant of time-consuming EI combination therapy^[16-18]. As sustained hemostasis is the goal of endoscopic therapy, we tried to identify factors which predicted recurrent bleeding after achieving initial hemostasis with EI monotherapy. Therefore, an additional hemostatic method to EI, or initial thermocoagulation, sclerosant injection or clips is warranted in such high-risk patients to ensure better hemostatic efficacy.

MATERIALS AND METHODS

Patient selection

Based on previous validations, those ulcers with spurting bleeding (I a), oozing bleeding (I b), non-bleeding visible vessel (NBVV, II a) and adherent clots (II b) were high-risk ulcers according to the Forrest classification and should be considered for endoscopic therapy^[4,19]. From October 2006 to April 2008 in the Medical Center, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, we enrolled patients with high-risk ulcers (I, II a and II b) who achieved initial hemostasis with EI monotherapy (epinephrine solution, 1:10000) into this study. Patients who failed to achieve hemostasis during EI monotherapy or received endoscopic combination therapy were excluded. Moreover, patients with malignant ulcers were also excluded. Pharmacotherapy with proton pump inhibitors (PPIs) in these patients was also recorded.

Clinical, laboratory and endoscopic assessments

We analyzed the possible factors which predicted recurrent bleeding in patients with successful initial hemostasis. The clinical, laboratory and endoscopic variables investigated included age, sex, Forrest class, ulcer size, ulcer location, hemoglobin level, blood transfusion, difficulty in the injection approach, injection dose, patient status including outpatient (in the emergency room due to ulcer bleeding) and inpatient (development of ulcer bleeding during admission) and bleeding presentation including severe bleeding signs (SBS; hematemesis or hematochezia) or mild bleeding signs (MBS; coffee ground vomitus or melena). Shock status was defined as either a systolic blood pressure of less than 90 mmHg, or less than 100 mmHg plus a pulse rate of more than 100

beats per minute. The clinical risk status of the patients was assessed by means of the American Society of Anesthesiology (ASA) classification^[20]. That is, ASA I = healthy patient, ASA II = patient with mild systemic disease without functional limitation, ASA III = severe systemic disease with definite functional limitation, ASA IV = severe systemic disease that is a constant threat to life, and ASA V = moribund patient not expected to survive for more than 24 h with or without surgery. The hemoglobin level was recorded before blood transfusion and endoscopic therapy. The total amount of packed red blood cells (pRBC) transfused was recorded until endoscopic hemostasis was achieved. Use or non-use of nonsteroidal anti-inflammatory drugs (NSAID) and aspirin was also recorded. The accessibility of injection therapy was categorized into an easy or difficult approach depending on the location of the ulcers. Peptic ulcers located in the lesser curvature and posterior wall of the gastric body and posterior wall of the duodenum were regarded as those that required a difficult approach for injection therapy. Peptic ulcers located in areas other than the above-mentioned were regarded as easy approach. Rebleeding was defined as the recurrence of bleeding within 2 wk of initial hemostasis.

Statistical analysis

Univariate analysis for possible factors predicting recurrent bleeding was performed using the Pearson χ^2 test and Fisher's exact test for categorical variables and the Student's *t* test for continuous variables. Variables with a $P < 0.05$ were considered statistically significant. Variables with a $P < 0.4$ in the univariate analysis were used for multiple logistic regression analysis with backward stepwise correction and were considered independent predictors of recurrent bleeding with a $P < 0.05$.

RESULTS

From October 2006 to April 2008, a total of 662 sessions of EI-based procedures to treat upper gastrointestinal bleeding were recorded in our computerized medical record system. After excluding patients who underwent endoscopic combination therapy, endoscopic hemostasis failure, and those who had malignant ulcer bleeding or Mallory-Weiss tear bleeding, a total of 175 patients with high-risk ulcers (I, II a and II b) who achieved initial hemostasis were enrolled. All these patients received intravenous PPI therapy during the acute bleeding period followed by oral PPIs to maintain hemostasis. Our records indicated that 144 patients (82.3%) achieved sustained hemostasis and 31 patients (17.7%) suffered from recurrent bleeding. Univariate analysis revealed that older age (age ≥ 60 years), advanced ASA status (category III, IV and V), shock, severe anemia (hemoglobin < 80 g/L), injection dose ≥ 12 mL and SBS were risk factors of recurrent bleeding (Table 1). However, backward stepwise correction (Table 2) revealed that only older age ≥ 60 years, odds ratio (OR) 5.11, 95% confidence interval (CI): 1.34, 19.48,

Table 1 Predictors of recurrent bleeding after epinephrine injection therapy in the univariate analysis

	Sustained hemostasis	Recurrent bleeding	P value
Patient number	144	31	
Age (yr)	63.7 (±14.4)	68.0 (±11.3)	0.035
< 60	55	5	0.019
≥ 60	89	26	
Sex			0.375
Male	100	24	
Female	44	7	
ASA category			0.006
I, II	44	2	
III, IV, V	100	29	
Shock			0.003
Negative	119	18	
Positive	25	13	
Forrest class			0.973
Active bleeding (I a, I b)	98	21	
Recent bleeding (II a, II b)	46	10	
Ulcer size (cm)			1.000 ¹
< 2	128	28	
≥ 2	16	3	
Injection approach			0.689
Easy	80	16	
Difficult	64	15	
Ulcer location			0.512
Stomach	79	15	
Duodenum	65	16	
Pre-endoscopic blood transfusion (mL)	658 ± 475	758 ± 463	0.277
< 1000	92	19	0.785
≥ 1000	52	12	
Hemoglobin (g/dL)	9.5 ± 2.4	6.6 ± 1.7	< 0.001
≥ 8	104	6	< 0.001
< 8	40	25	
Injection dose (mL)	8.7 ± 4.1	10.4 ± 5.0	0.057
< 12	127	21	0.011
≥ 12	17	10	
Bleeding signs			< 0.001
Mild	119	16	
Severe	25	15	
Patient status			0.076
Outpatient	81	12	
Inpatient	63	19	
NSAID/aspirin			0.738
User	51	10	
Non-user	93	21	

¹The value was obtained according to Fisher's exact test based on an expectation value < 5. NSAID: Nonsteroidal anti-inflammatory drug.

hemoglobin < 80 g/L (OR 13.44, 95% CI: 4.29, 42.13), injection dose ≥ 12 mL (OR 5.72, 95% CI: 1.69, 19.38) and SBS (OR 5.46, 95% CI: 1.89, 15.79) were independent predictors. All 31 rebleeding patients received repeated endoscopic therapies, and only 14 of them achieved permanent hemostasis. The rest suffered from recurrent bleeding and 10 underwent surgery. In summary, among the 31 patients who re-bleeded after initial endoscopic hemostasis with EI alone, 15 (18/31, 48.4%) encountered delayed hemostasis causing major complications such as sepsis, hypovolemic shock, and renal and respiratory failure, and 13 (13/31, 41.9%) died of these complications (Table 3). The overall clinical course of the 175 patients is listed in Figure 1.

Table 2 Predictors of recurrent bleeding after epinephrine injection therapy from stepwise logistic regression in the multivariate analysis

	Odds ratio	95% CI	P value
Age (yr)			
≥ 60 vs < 60	5.11	1.34-19.48	0.017
Hemoglobin (g/dL)			
< 8 vs ≥ 8	13.44	4.29-42.13	< 0.001
Bleeding signs			
Severe vs mild	5.46	1.89-15.79	0.002
Injection dose (mL)			
≥ 12 vs < 12	5.72	1.69-19.38	0.005

Variables of P < 0.4 were used in the multivariate analysis. CI: Confidence interval.

Table 3 The outcome of 31 patients with rebleeding after initial hemostasis using epinephrine injection therapy

Outcome of rebleeding patients	No. of patients (n = 31)
Surgery	10 (32.2%)
Major complications ¹	15 (48.4%)
Sepsis	8
Renal failure	2
Respiratory failure	8
Hypovolemic shock	2
Death	13 (41.9%)

¹Some patients suffered 2 or more major complications related to recurrent bleeding.

DISCUSSION

Due to medical progress in the management of ulcer hemorrhage, pharmacotherapy with PPIs and endoscopic hemostasis are standard treatments. PPIs are the first choice of pharmacotherapy to control ulcer bleeding at present due to their strong inhibition of acid secretion and promotion of platelet aggregation^[21]. PPIs have also been demonstrated to reduce rebleeding, the need for surgery and repeated endoscopic therapy^[22]. With regard to endoscopic therapy, this treatment also reduces the occurrence of rebleeding, the need for surgery and the morbidity and mortality of patients. When bleeding recurs, however, repeated endoscopic therapy may either prevent patients from undergoing surgery or delay surgical hemostasis^[23,24]. Therefore, the most important goal of endoscopic therapy is to initially achieve permanent hemostasis. Recently, numerous meta-analyses have indicated that adding a second procedure, such as a second injectate (alcohol, thrombin, sclerosant or fibrin glue), thermocoagulation or clips to EI significantly reduced rebleeding, surgery and mortality compared with EI alone in high-risk ulcer patients^[11-15]. EI alone is not recommended in the management of bleeding ulcers; however, the reality is that endoscopic hemostasis with EI alone is still commonly practiced^[16-18]. There are several reasons for this: first, injection monotherapy is a simple and effective hemostatic method (82.3% in the current study). Second, EI combination therapy is

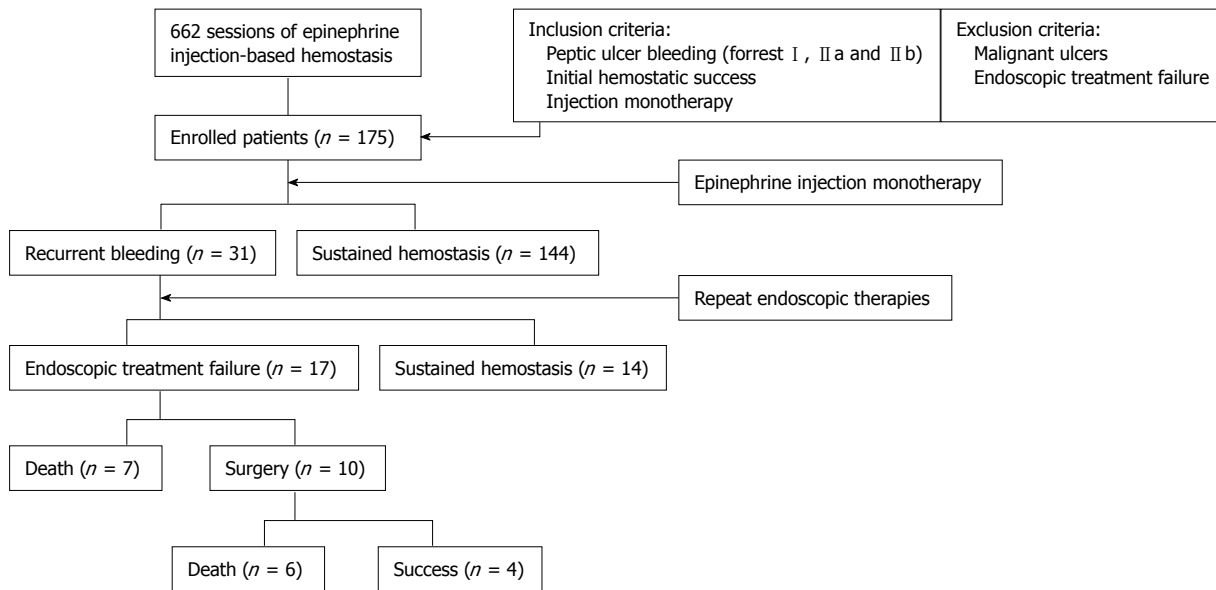


Figure 1 The clinical course of 175 patients with successful initial hemostasis after endoscopic epinephrine injection monotherapy.

a relatively time-consuming procedure, so patients may not tolerate or complete the process, particularly those in a hemodynamically unstable status. Third, thermotherapy such as argon plasma coagulation (APC) or mechanical hemostasis with clips may not be available in every endoscopic unit, particularly in local hospitals. Therefore, to identify predictors of recurrent bleeding in high-risk ulcer patients after EI alone may justify the benefit of endoscopic combination therapy or initial replacement by thermocoagulation or clips for a better treatment outcome. Those patients with such risk factors treated with EI only should be closely monitored or referred to other hospitals with a well-equipped endoscopic unit. From the high-risk ulcer patients treated by PPIs pharmacotherapy and EI alone in our study, we found older age (≥ 60 years), advanced ASA categories (III, IV and V), shock, severe anemia (hemoglobin < 80 g/L), injection dose ≥ 12 mL and SBS were the factors which predicted rebleeding. Older age, severe anemia, high injection dose and SBS were independent predictors in multivariate analysis.

Compared to ulcers with NBVV or black spots, active ulcer bleeding tends to rebleed if left untreated. After successful endoscopic hemostasis and administration of PPIs, there were no statistical differences observed in this study. Severe anemia and SBS were relevant to the amount of blood loss and the severity of ongoing bleeding, and were risk factors for recurrent bleeding. The amount of blood transfused before endoscopic therapy may not correlate well with the severity of blood loss. In our hospital, a 24-h emergency endoscopy service is provided and patients often undergo early therapeutic endoscopy within 24 h of either visiting the emergency room or the occurrence of bleeding after admission. Thus, the amount transfused prior to early endoscopy cannot be considered as a risk factor of rebleeding. As for the use of large and small volumes of EI in bleeding ulcers, there are two prospective studies which refer to the hemostatic

effectiveness of injection volume. In these studies, the injection of a larger volume might reduce the rate of recurrent bleeding compared to a smaller volume in a prospective design^[25,26]. On the other hand, the need for a higher injection dose to arrest bleeding might imply a difficult hemostasis and a higher risk of recurrent bleeding from a retrospective viewpoint. In our study, an injection dose ≥ 12 mL was an independent risk factor of recurrent bleeding.

NSAID and aspirin also cause peptic ulcer bleeding. Prior use of NSAID/aspirin was reported to increase the risk of rebleeding in bleeding ulcer patients^[27,28]. If the use of NSAID is discontinued, PPI therapy is very effective in treating NSAID-related ulcers and preventing further bleeding.

It is well known that *Helicobacter pylori* (*H. pylori*) infection can cause peptic ulcers. The detection of *H. pylori* was not performed in our study as these patients were in an acute bleeding phase. The rapid urease test during the acute bleeding phase is unreliable for the detection of *H. pylori* infection^[29]. Furthermore, Schilling *et al.*^[30] also revealed that *H. pylori* infection does not affect the early rebleeding rate in patients with peptic ulcer bleeding after successful endoscopic hemostasis, however, patients should be tested and treated for *H. pylori* infection once their condition has stabilized to prevent recurrent ulcers.

EI monotherapy is commonly practiced in endoscopic hemostasis due to its good efficacy, and because it is a simple and time-saving technique^[2-4]; however, it should be replaced by combination therapy, clips, sclerosant injection or thermocoagulation based on more recent evidence. Sclerosant injection, clips or thermocoagulation alone or in combination with EI are more effective methods than EI alone. Although we achieved sustained hemostasis in 82.3% of our patients with bleeding ulcers treated by endoscopic EI monotherapy, 31 patients suffered from recurrent bleeding. The outcome of the patients with re-

bleeding was discouraging as 15 patients (48.4%) suffered from major complications and 13 patients (41.9%) died of complications. Among the 31 rebleeding patients, 10 patients underwent surgical hemostasis but only 4 patients survived. Although these rebleeding patients often had underlying major diseases, to achieve sustained hemostasis using sclerosant, thermocoagulation, clips or EI combination as soon as possible would allow these patients to have a better prognosis. Therefore, we suggest that all patients with high-risk ulcers should undergo sclerosant injection, thermocoagulation or clips in index endoscopy because they are more effective and time-saving. EI followed by thermocoagulation, clips or another injectate should also be considered, however, these are more time-consuming and some patients cannot tolerate or complete the procedures. Unless sclerosant, APC or clips are unavailable, EI alone is not recommended, particularly in older patients (> 60 years), SBS, severe anemia, and those in need of a higher EI dose to arrest bleeding during endoscopic therapy. Additional endoscopic therapies to EI are mandatory or these patients should be referred to a hospital with a well-equipped endoscopic unit for close monitoring.

In conclusion, endoscopic EI monotherapy in patients with high-risk ulcers should be avoided. Initial hemostasis with thermocoagulation, clips or additional hemostasis after EI is mandatory, particularly in older patients, SBS, severe anemia and where a higher injection dose in need. Then, it is possible to ensure that such patients have a better hemostatic status and will avoid subsequent rebleeding, surgery, morbidity and mortality.

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COMMENTS

Background

Recent studies have revealed that thermocoagulation, sclerosant injection or clips alone, or combined with epinephrine injection (EI) are superior to EI alone in preventing rebleeding, surgery and mortality. EI alone is not recommended. However, the reality is that EI monotherapy to arrest ulcer bleeding is still common practice, in part, because it is a relatively simple and effective hemostatic method and because some patients are intolerant of time-consuming EI combination therapy.

Research frontiers

Sustained hemostasis is the goal of endoscopic therapy. This study identified the factors which predicted rebleeding if patients with high-risk ulcers were treated using EI alone to achieve initial hemostatic status.

Innovations and breakthroughs

Endoscopic EI monotherapy in patients with high-risk ulcers should be avoided. Initial hemostasis with thermocoagulation, clips or additional hemostasis after EI is mandatory, particularly in older patients, SBS, severe anemia, and where a higher injection dose is needed to prevent subsequent rebleeding, surgery, morbidity and mortality.

Applications

This article further emphasized the need to follow the existing guidelines for the treatment of high-risk ulcers to possibly avoid a poor outcome when EI is performed alone.

Terminology

High-risk ulcers refer to ulcers with active bleeding, or with non-bleeding visible

vessels or adherent clots, and endoscopic therapy is necessary in these ulcers to prevent further bleeding.

Peer review

The clinical study focused on identification of predictors of rebleeding after initial epinephrine hemostasis in the upper gastrointestinal tract. The statistical approach revealed age, severe bleeding signs, hemoglobin, and epinephrine injection dose more than 12 mL as predictors.

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