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ORIGINAL ARTICLE

Retrospective Cohort Study

Predictors of re-bleeding after endoscopic hemostasis for delayed post-endoscopic sphincterotomy bleeding

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Abstract

AIM: To predict the re-bleeding after endoscopic hemostasis for delayed post-endoscopic sphincterotomy (ES) bleeding.

METHODS: Over a 15-year period, data from 161 patients with delayed post-ES bleeding were retrospectively collected from a single medical center. To identify risk factors for re-bleeding after initial successful endoscopic hemostasis, parameters before, during and after the procedure of endoscopic retrograde cholangiopancreatography were analyzed. These included age, gender, blood biochemistry, comorbidities, endoscopic diagnosis, presence of periampullary diverticulum, occurrence of immediate post-ES bleeding, use of needle knife precut sphincterotomy, severity of delayed bleeding, endoscopic features on delayed bleeding, and type of endoscopic therapy.

RESULTS: A total of 35 patients (21.7%) had re-bleeding after initial successful endoscopic hemostasis for delayed post-ES bleeding. Univariate analysis revealed that malignant biliary stricture, serum bilirubin level of greater than 10 mg/dL, initial bleeding severity, and bleeding diathesis were significant predictors of re-bleeding. By multivariate analysis, serum bilirubin level of greater than 10 mg/dL and initial bleeding severity remained significant predictors. Re-bleeding was controlled by endoscopic therapy in a single (n = 23) or multiple (range, 2-7; n = 6) sessions in 29 of the 35

patients (82.9%). Four patients required transarterial embolization and one went for surgery. These five patients had severe bleeding when delayed post-ES bleeding occurred. One patient with decompensated liver cirrhosis died from re-bleeding.

CONCLUSION: Re-bleeding occurs in approximately one-fifth of patients after initial successful endoscopic hemostasis for delayed post-ES bleeding. Severity of initial bleeding and serum bilirubin level of greater than 10 mg/dL are predictors of re-bleeding.

Key words: Delayed bleeding; Endoscopic hemostasis; Endoscopic sphincterotomy; Predictors; Re-bleeding

Core tip: Re-bleeding occurs in about one-fifth of patients after initial successful endoscopic hemostasis for delayed post-ES bleeding. Predictors of re-bleeding has not been studied. Our study reveals malignant biliary stricture, serum bilirubin level of greater than 10 mg/dL, initial bleeding severity, and bleeding diathesis were significant predictors of re-bleeding. These patients often require multiple endoscopic treatments, transarterial embolization or surgery to control the bleeding.

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INTRODUCTION

Endoscopic sphincterotomy (ES) is the cornerstone of therapeutic endoscopic retrograde cholangiopancreatography (ERCP). Sphincterotomy wound bleeding is its most frequent complication[1,2]. The incidence of clinically significant post-ES bleeding ranges between 0.76%-2% when it is defined as overt gastrointestinal bleeding with decreased hemoglobin level[1,3-5]. Post-ES bleeding is classified as immediate or delayed, based on the time of its presentation[6]. Immediate post-ES bleeding occurs during the procedure, and can therefore be observed by the endoscopist on site[7]. However, endoscopically discernible bleeding may not be clinically significant[8]. The majority of immediate post-ES bleeding is self-limited and can usually be managed conservatively[9-11]. Wilcox *et al*[9] reported that the pattern of bleeding following ES does not predict the risk of delayed bleeding.

Delayed post-ES bleeding occurs after the completion of ERCP[7]. These patients generally have clinical manifestations of overt gastrointestinal bleeding, such as melena, hematemesis, or hematochezia, and decreased hemoglobin level that require immediate endoscopic hemostasis[12-16]. Some patients re-bleed after initial successful treatment and need repeated endoscopic hemostatic therapy, transarterial embolization (TAE) or even surgery to control bleeding. However, factors affecting the success of endoscopic treatment for delayed post-ES bleeding has rarely been studied[17]. Determining the risk factors for re-bleeding after endoscopic treatment for delayed post-ES bleeding may be useful for monitoring or establishing additional hemostatic measures in high-risk patients. In this retrospective study, we analyzed factors predicting re-bleeding after initial successful endoscopic hemostasis for delayed post-ES bleeding.

MATERIALS AND METHODS

Definitions

Immediate post-ES bleeding: Any hemorrhage caused by ES that warrants endoscopic hemostasis during ERCP. Delayed post-ES bleeding: Any hemorrhage occurring after completion of ERCP, manifested as melena, hematemesis or hematochezia, with a decrease in hemoglobin level from the baseline. Clinically significant bleeding and its severity was classified according to Cotton *et al*[18], as follows: mild bleeding was defined as overt bleeding with a decrease of hemoglobin level less than 3 g/dL, without the need for transfusion; moderate bleeding was defined blood transfusion of 4 units or less but without the need for angiographic intervention or surgery; *severe bleeding* was defined blood transfusion of 5 units or more, or the need for angiographic or surgical intervention; re-bleeding was defined as recurrent bleeding after initial successful endoscopic hemostasis for delayed post-ES bleeding that requires interventions.

Bleeding diathesis was defined as the presence of thrombocytopenia (platelet count < 80000/μL), coagulopathy (prolonged prothrombin time > 3 s from the control), or chronic renal failure requiring maintenance hemodialysis[19].

Patients and endoscopic procedures

Between January 1999 and September 2014, 7612 ES procedures were carried out at Chang Gung Memorial Hospital. Of these, data from 161 patients (2.1%) with delayed post-ES bleeding were retrospectively collected from the hospital database of our Therapeutic Endoscopy Center. ES procedures were similar to those described in our previous study[15]. The study protocol (number 103-3829B) was discussed and approved by the Institutional Review Board of the Chang Gung Hospital.

Hemostatic treatment for delayed post-ES bleeding was performed by using a side-viewing endoscope

(JF-240 or JF-260v, Olympus, Tokyo, Japan). The settings and application of endoscopic treatment were similar to those used for peptic ulcer bleeding[20,21]. The types of endoscopic therapy for post-ES bleeding could be either monotherapy or combination therapy at the endoscopists' discretion. Monotherapy denoted use of only one endoscopic technique for hemostasis, whereas combination therapy used more than one endoscopic technique. Initial endoscopic treatment for delayed post-ES bleeding was considered successful when there was no clinical evidence of bleeding after the procedure.

Monotherapy (n = 72) indicated either injection with diluted epinephrine (n = 52) or thermotherapy (n = 20). Diluted epinephrine (1:10000) was injected in 0.5-2 mL aliquots into and around the bleeder at the sphincterotomy site until bleeding was controlled. Thermotherapy indicated one of the four modes, heat probe coagulation (n = 11), bipolar coagulation (gold probe, n = 6), monopolar coagulation (hot biopsy forceps, n = 2), and argon plasma coagulation (APC, n = 1). Patients receiving combination therapy (n = 89) had both epinephrine injection and thermotherapy (n = 85), both epinephrine injection and hemoclipping (n = 1), or all three modes (n = 3).

Clinical and laboratory parameters before, during and after ERCP were analyzed to identify risk factors for re-bleeding. These included age, gender, blood biochemistry, co-morbidities, endoscopic diagnosis, presence of peri-ampullary diverticulum, occurrence of immediate post-ES bleeding, use of needle knife precut sphincterotomy, severity of delayed bleeding, endoscopic features on delayed bleeding, and type of endoscopic therapy.

Statistical analysis

Statistical analysis was performed with chi-square test or Fisher exact test and independent Student t-test for categorical and continuous variables, between groups of patients with and without re-bleeding. Mann-Whitney U test and Wilcoxon test were used for nonparametric analysis. Continuous variables are shown as mean with range. Logistic regression analysis was performed to identify predictor of re-bleeding after treatment. Statistical analyses were performed using SPSS software (version 20.0; SPSS, Inc., Chicago, IL, United states). A two-tailed P value of < 0.05 was considered statistically significant.

RESULTS

A total of 35 out of 161 patients (21.7%) had re-bleeding after initial successful endoscopic hemostasis for delayed post-ES bleeding. Their mean age was 63 years old; 65.7% were male. Table 1 lists their demographics, laboratory and clinical data. There was no difference between patients with or without re-bleeding in terms of their age and gender. Mean serum bilirubin level was significantly higher in patients with re-bleeding (10.9 mg/dL *vs* 6.5 mg/dL, P = 0.002). The presence of decompensated liver cirrhosis (11.4% *vs* 3.2%, P = 0.047) and bleeding diathesis (45.8% *vs* 17.5%, $P < 0.001$) were also associated with higher risk of re-bleeding.

Table 1 Associations between re-bleeding and patient characteristics *n* (%)

	Re-bleeding (n = 35)	No re-bleeding (n = 126)	P value
Age (yr)	63.0 (52.0-70.0)	57.0 (46.5-71.0)	0.121
Sex (male)	23 (65.7)	82 (65.1)	0.944
White blood cell count (× $10^3/\mu L$)	8.1 (5.6-10.0)	8.1 (6.0-10.7)	0.673
Platelet count (× $10^3/\mu L$)	225 (122-262)	215 (160-268)	0.320
INR	1.1 (1.0-1.5)	1.1 (1.0-1.2)	0.075
Total bilirubin (mg/dL)	10.9 (2.3-22.3)	6.5 (1.1-15.8)	0.002
ESRD	3 (8.6)	10 (7.9)	1.000
Decompensated liver cirrhosis	4 (11.4%)	4 (3.2)	0.047
Use of anti-platelet regimen			
Before ES	3 (8.6)	3 (2.4)	0.117
Within 3 d after ES	2 (5.7)	2 (1.6)	0.206
Cholangitis before ES	13 (37.1)	58 (46.0)	0.349
Bleeding diathesis	16 (45.8)	22 (17.5)	< 0.001

ESRD: End stage renal disease; INR: International normalized ratio; ES: Endoscopic sphincterotomy.

ERCP procedure-related parameters are listed in Table 2. Endoscopic diagnosis included choledocholithiasis (51.4%), malignant biliary stricture (31.4%), benign biliary stricture (8.6%), biliary leakage (0%), and others (11.4%). Re-bleeding occurred more often in patients with malignant biliary stricture (31.4% *vs* 5.6%, $P < 0.001$). Presence of periampullary diverticulum, occurrence of immediate post-ES bleeding, or use of needle knife precut sphincterotomy, did not differ significantly between patients with or without re-bleeding.

Initial delayed bleeding occurred within 2 h to 15 d (mean, 3.4 d) in our patients. Among the 35 patients who had re-bleeding after initial successful hemostatic therapy, 19 (54.3%) patients had severe bleeding in their first event, 15 (42.9%) moderate, and 1 (2.9%) mild (Table 3). Those with severe bleeding had a higher likelihood of re-bleeding (54.3% *vs* 11.9%, $P < 0.001$). Bleeding stigmata with non-bleeding visible vessel was significantly associated with re-bleeding (11.4% *vs* 3.2%, P = 0.047) while non-bleeding red spots was not (0% *vs* 11.1%, P = 0.041). The risk of re-bleeding was not related to what mode of hemostatic therapy employed whether monotherapy or in combination.

The result of univariate and multivariate analyses is in Table 4. Risk factors associated with re-bleeding were the presence of malignant biliary stricture, serum bilirubin level of greater than 10 mg/dL, bleeding diathesis, and bleeding severity by univariate

Table 2 Associations between re-bleeding and endoscopic retrograde cholangopancreatography *n* (%)

	Re-bleeding (*n* = 35)	No re-bleeding (*n* = 126)	*P* value
Endoscopic diagnosis			
Choledocholithiasis	18 (51.4)	86 (69.0)	0.066
Malignant biliary stricture	11 (31.4)	7 (5.6)	< 0.001
Benign biliary stricture	3 (8.6)	8 (7.1)	0.706
Biliary leak	0 (0.0)	1 (0.8)	1.000
Others	4 (11.4)	24 (19)	0.571
Periampullary diverticulum	6 (17.1)	23 (18.3)	0.880
Immediate post-ES bleeding	14 (40.0)	40 (31.7)	0.360
Needle knife precut sphincterotomy	6 (17.1)	13 (10.3)	0.372

ERCP: Endoscopic retrograde cholangopancreatography; INR: International normalized ratio; ES: Endoscopic sphincterotomy.

Table 3 The association between re-bleeding and bleeding stigmata/treatment methods at initial endoscopic treatment for delayed bleeding *n* (%)

	Re-bleeding (*n* = 35)	No re-bleeding (*n* = 126)	*P* value
Bleeding severity			< 0.001
Mild	1 (2.9)	46 (36.5)	
Moderate	15 (42.9)	65 (51.6)	
Severe	19 (54.3)	15 (11.9)	
Features of ES wound			
Active bleeding	27 (77.1)	85 (67.5)	0.271
Non-bleeding visible vessel	4 (11.4)	4 (3.2)	0.047
Non-bleeding adherent clot	4 (11.4)	23 (18.3)	0.517
Non-bleeding red spots	0 (0.0)	14 (11.1)	0.041
Type of endoscopic therapy			
Monotherapy	13 (37.1)	59 (46.8)	0.342
Epinephrine injection	7 (20.0)	45 (35.7)	0.102
Thermocoagulation	6 (17.1)	14 (11.1)	0.385
Combination therapy[1]	22 (65.7)	67 (53.2)	0.342
Thermocoagulation	21 (60.0)	64 (50.8)	0.347
Hemoclipping	0 (0.0)	1 (0.8)	1.000
Thermotherapy + hemoclipping	1 (2.9)	2 (1.6)	1.000

[1]Including dilute epinephrine injection plus one of the three types of therapy. ES: Endoscopic sphincterotomy.

analysis. Multivariate analysis, however, revealed only two parameters, serum bilirubin level and bleeding severity, remained statistically significant.

Outcomes of endoscopic hemostatic therapy for re-bleeding are listed in Table 5. In 29 patients (82.9%), re-bleeding was controlled after a single (*n* = 23) or multiple (range, 2-7; *n* = 6) treatment sessions. Patients with severe re-bleeding required multiple sessions more often than those with moderate and mild re-bleeding (15.2% *vs* 2.5% *vs* 0%, respectively, *P* = 0.002). Transarterial embolization or surgery was required only in five patients with severe re-bleeding. One patient (2.8%) with decompensated liver cirrhosis died after three sessions of endoscopic therapy.

DISCUSSION

In patients with peptic ulcer bleeding, re-bleeding after initial endoscopic hemostasis is an important predictor of mortality[22]. In patients receiving therapeutic ERCP, the incidence of post-ES delayed bleeding is up to 2% but re-bleeding after successful endoscopic hemostatic therapy goes to 21.7% of the time by our estimate. The predictors of re-bleeding have not been addressed in the literature. Our study revealed that serum bilirubin level of greater than 10 mg/dL and bleeding severity are the two significant predictors of re-bleeding. Two other predictors, the presence of malignant biliary stricture and bleeding diathesis, were not statistically significant after multivariate analysis.

Patients with malignant biliary stricture usually, but not always, have a higher serum bilirubin level than those with common bile duct stones. Malignant biliary obstruction often leads to difficult cannulation for which needle knife pre-cut sphincterotomy is frequently performed (5/18 *vs* 13/143, *P* = 0.033). In our study, however, use of this technique was not associated with higher risk of re-bleeding. Thus prolonged bile duct obstruction, irrespective of its etiology, as manifested with deep jaundice is a more significant predictor of re-bleeding. The reason for this association remains to be investigated.

Our study also showed that patients with severe initial post-ES delayed bleeding have a higher rate of re-bleeding. Bleeding diathesis, defined as presence of thrombocytopenia, coagulopathy, or chronic renal failure requiring maintenance hemodialysis, was a significant predictor of re-bleeding by univariate analysis, and yet not statistically significant by multivariate analysis. Ferreira *et al*[14] reported patients with coagulopathy tend to have more severe post-ES delayed bleeding and thus a higher re-bleeding rate. Our finding suggests severe bleeding, most likely from injury of an arteriole whether discernible or not after ES, is the culprit of re-bleeding, a clinical scenario similar to the presence of Forrest IIa-b ulcer in predicting the risk of re-bleeding. On the other hand, bleeding diathesis can be, and usually has been, corrected before endoscopic hemostatic therapy. This will inevitably reduce its predictive power for re-bleeding.

There is no consensus for the optimal endoscopic hemostatic technique post-ES bleeding[7]. Methods including local injection therapy, thermotherapy (APC, bipolar or heat probe devices) and placement of hemoclips or covered self-expandable metal stent, either alone or in combination, have been reported with varying rates of success[9,23-26]. In our unpublished experience, a monopolar device such as a hot biopsy forceps (Olympus) was effective for post-ES bleeding (60 or 80 W, effect 2, soft coagulation mode). In

Table 4 Univariate and multivariate analyses for predictors of re-bleeding

Predictor	Univariate			Multivariate		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Malignant biliary stricture						
No	1					
Yes	7.79	2.74-22.14	< 0.001			
Serum bilirubin level[1]						
≤ 10	1			1		
> 10	4.7	2.06-10.72	< 0.001	3.55	1.39-9.11	0.008
Bleeding severity						
Mild	1			1		
Moderate	10.62	1.354-83.22	0.025	10.97	1.379-87.18	0.024
Severe	58.27	7.18-472.79	< 0.001	48.74	5.90-402.93	< 0.001
Bleeding diathesis						
No	1					
Yes	3.98	1.77-8.94	< 0.001			

[1]A serum bilirubin level > 10 mg/dL was associated with area under the receiver operating characteristic curve of 0.678 (95%CI: 0.57-0.78, $P = 0.002$).

Table 5 Treatment outcomes *n* (%)

	Overall (*n* = 35)
Successful endoscopic hemostasis	29 (82.9)
Only 1 session	23
More than 1 session	6
Mean endoscopic session (range)	2.34 (2-7)
TAE/surgery required for hemostasis	4/1 (14.3)
Bleeding-related death	1 (2.8)

TAE: Transarterial embolization.

treating bleeding ulcer, monopolar coagulation was superior not only in primary hemostasis but also in reducing re-bleeding rate to the conventional therapy with local injection followed by heat probe thermocoagulation[20]. Katsinelos *et al*[27] also reported that monopolar coagulation was an effective treatment method for post-ES bleeding when injection therapy failed. Further studies are needed to address this issue.

This study has several limitations. It is a retrospective design including patients from a single medical center. However, to our knowledge, this is the largest study to date and there has been no prospective study in the literature. Secondly, a higher percentage (33.5%, 54/161) of our patients received endoscopic hemostasis for immediate post-ES bleeding. It is not clear whether prior treatment for immediate post-ES bleeding impacted on the rate of delayed bleeding and bleeding severity. Thirdly, all patients with delayed bleeding in our study received endoscopic hemostatic therapy, although ES wound with non-bleeding red spots may be of low risk of re-bleeding even without prophylactic treatment.

In conclusion, our study showed two predictors of re-bleeding for patients with post-ES delayed bleeding after initial successful endoscopic therapy were serum bilirubin level of greater than 10 mg/dL and bleeding severity. We propose use of these variables for risk stratification of these patients, and for future study design investigating the appropriate management strategy to reduce re-bleeding risk.

COMMENTS

Background

Delayed post-endoscopic sphincterotomy (ES) bleeding occurs after the completion of endoscopic retrograde cholangiopancreatography (ERCP). Most patients need endoscopic treatment for delayed bleeding but some of them will have re-bleeding. However, risk factors for re-bleeding has rarely been studied.

Research frontiers

Determining the risk factors for re-bleeding after endoscopic treatment for delayed post-ES bleeding is useful for monitoring or establishing additional hemostatic measures in high-risk patients.

Innovations and breakthrough

The study results showed that serum bilirubin level of greater than 10 mg/dL and bleeding severity were the two independent risk factors for re-bleeding.

Applications

Patients with the risk factors should be carefully monitored after initial success of endoscopic treatment for delayed post-ES bleeding.

Terminology

ERCP is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat certain problems of the biliary or pancreatic ductal systems. ES is an extension to ERCP that the opening of the ampulla can be enlarged by a cut with an electrified wire called sphincterotome and access into the bile duct obtained.

Peer-review

This is a well done retrospective review looking at the incidence of rebleeding after treatment of acute bleeding at time of endoscopic sphincterotomy. The authors note that only serum bilirubin ⩾ 10 mg/dL and initial bleeding severity were predictors of rebleeding.

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