**Name of journal: *World Journal of Gastroenterology***

**ESPS Manuscript NO: 21569**

**Manuscript type: ORIGINAL ARTICLE**

***Retrospective cohort study***

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

Lee MH *et al.* Re-bleeding after treatment for sphincterotomy bleeding

Mu-Hsien Lee, Yung-Kuan Tsou, Cheng-Hui Lin, Ching-Song Lee, Nai-Jen Liu, Kai-Feng Sung, Hao-Tsai Cheng

**Mu-Hsien Lee, Yung-Kuan Tsou, Cheng-Hui Lin, Ching-Song Lee, Nai-Jen Liu, Kai-Feng Sung, Hao-Tsai Cheng,** Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taipei 105, Taiwan

**Author contributions:** Tsou YK designed research and analyzed data; Lin CH, Lee CS, Liu NJ, Sung KF and Cheng HT performed research and contributed analytic tools; Lee MH wrote the paper and analyzed data.

**Institutional review board statement:** The study was reviewed and approved by Institutional Review Board of Chang Gung Hospital.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors have no financial disclosures to declare and no conflicts of interest to report.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at flying@adm.cgmh.org.tw. Participants gave informed consent for data sharing.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Yung-Kuan Tsou, MD,** Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 5 Fu-Shin Street, Kweishan, Taoyuan 333, Taiwan. flying@adm.cgmh.org.tw

**Telephone:** +886-3-3281200-8108

**Fax:** +886-3-3272236

**Received:** July 21, 2015

**Peer-review started:** July 30, 2015

**First decision:** September 29, 2015

**Revised:** October 30, 2015

**Accepted:** December 30, 2015

**Article in press:**

**Published online:**

**Abstract**

**AIM:** Topredict 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, 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.

**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

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Lee MH, Tsou YK, Lin CH, Lee CS, Liu NJ, Sung KF, Cheng HT. Predictors of re-bleeding after endoscopic treatment for delayed post-endoscopic sphincterotomy bleeding. *World J Gastroenterol* 2015; In press

**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. reported that the pattern of bleeding following ES does not predict the risk of delayed bleeding[9].

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.

ERCP procedure-related parameters are listed in Table 2. Endoscopic diagnosis included choledocholithiasis (51.4%), malignant biliary stricture (31.4%), benign biliary stricture (5.7%), 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 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 80W, effect 2, soft coagulation mode). In 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.

**REFERENCES**

1 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]

2 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]

3 **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423 [PMID: 11232684 DOI: 10.1111/j.1572-0241.2001.03594.x]

4 **Christensen M**, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. *Gastrointest Endosc* 2004; **60**: 721-731 [PMID: 15557948 DOI: 10.1016/S0016-5107(04)02169-8]

5 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10 [PMID: 9684657 DOI: 10.1016/S0016-5107(98)70121-X].]

6 **ASGE Standard of Practice Committee**, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, Ben-Menachem T, Cash BD, Decker GA, Early DS, Fanelli RD, Fisher DA, Fukami N, Hwang JH, Ikenberry SO, Jue TL, Khan KM, Krinsky ML, Malpas PM, Maple JT, Sharaf RN, Shergill AK, Dominitz JA. Complications of ERCP. *Gastrointest Endosc* 2012; **75**: 467-473 [PMID: 22341094 DOI: [10.1016/j.gie.2011.07. 010](http://dx.doi.org/10.1016/j.gie.2011.07.010)]

7 **Ferreira LE**, Baron TH. Post-sphincterotomy bleeding: who, what, when, and how. *Am J Gastroenterol* 2007; **102**: 2850-2858 [PMID: 18042116 DOI: 10.1111/j.1572-0241.2007.01563.x]

8 **Freeman ML**. Adverse outcomes of ERCP. *Gastrointest Endosc* 2002; **56**: S273-S282 [PMID: 12447281 DOI: 10.1067/mge.2002.129028]

9 **Wilcox CM**, Canakis J, Mönkemüller KE, Bondora AW, Geels W. Patterns of bleeding after endoscopic sphincterotomy, the subsequent risk of bleeding, and the role of epinephrine injection. *Am J Gastroenterol* 2004; **99**: 244-248 [PMID: 15046211 DOI: 10.1111/j.1572-0241.2004.04058.x]

10 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Fennerty MB, DiSario JA, Ryan ME, Kortan PP, Dorsher PJ, Shaw MJ, Herman ME, Cunningham JT, Moore JP, Silverman WB, Imperial JC, Mackie RD, Jamidar PA, Yakshe PN, Logan GM, Pheley AM. Same-day discharge after endoscopic biliary sphincterotomy: observations from a prospective multicenter complication study. The Multicenter Endoscopic Sphincterotomy (MESH) Study Group. *Gastrointest Endosc* 1999; **49**: 580-586 [PMID: 10228255 DOI: 10.1016/S0016-5107(99)70385-8]

11 **Leung JW**, Chan FK, Sung JJ, Chung S. Endoscopic sphincterotomy-induced hemorrhage: a study of risk factors and the role of epinephrine injection. *Gastrointest Endosc* 1995; **42**: 550-554 [PMID: 8674926 DOI: 10.1016/S0016-5107(95)70009-9]

12 **Finnie IA**, Tobin MV, Morris AI, Gilmore IT. Late bleeding after endoscopic sphincterotomy for bile duct calculi. *BMJ* 1991; **302**: 1144 [PMID: 2043789 DOI: 10.1136/bmj.302.6785.1144]

13 **Gholson CF**, Favrot D, Vickers B, Dies D, Wilder W. Delayed hemorrhage following endoscopic retrograde sphincterotomy for choledocholithiasis. *Dig Dis Sci* 1996; **41**: 831-834 [PMID: 8625750 DOI: 10.1007/BF02091518]

14 **Ferreira LE**, Fatima J, Baron TH. Clinically significant delayed postsphincterotomy bleeding: a twelve year single center experience. *Minerva Gastroenterol Dietol* 2007; **53**: 215-223 [PMID: 17912183]

15 **Tsou YK**, Lin CH, Liu NJ, Tang JH, Sung KF, Cheng CL, Lee CS. Treating delayed endoscopic sphincterotomy-induced bleeding: epinephrine injection with or without thermotherapy. *World J Gastroenterol* 2009; **15**: 4823-4828 [PMID: 19824118 DOI: 10.3748/wjg.15.4823]

16 **Kim KO**, Kim TN, Kim SB, Lee JY. Characteristics of delayed hemorrhage after endoscopic sphincterotomy. *J Gastroenterol Hepatol* 2010; **25**: 532-538 [PMID: 20074163 DOI: 10.1111/j.1440-1746.2009.06123.x]

17 **Parlak E**, Dişibeyaz S, Köksal AŞ, Odemiş B, Saşmaz N, Şahin B. Factors affecting the success of endoscopic treatment of sphincterotomy bleeding. *Clin Res Hepatol Gastroenterol* 2013; **37**: 391-399 [PMID: 23164581 DOI: 10.1016/j.clinre.2012.10.004]

18 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]

19 **Van Os EC**, Kamath PS, Gostout CJ, Heit JA. Gastroenterological procedures among patients with disorders of hemostasis: evaluation and management recommendations. *Gastrointest Endosc* 1999; **50**: 536-543 [PMID: 10502177 DOI: 10.1016/S0016-5107(99)70079-9]

20 **Soon MS**, Wu SS, Chen YY, Fan CS, Lin OS. Monopolar coagulation versus conventional endoscopic treatment for high-risk peptic ulcer bleeding: a prospective, randomized study. *Gastrointest Endosc* 2003; **58**: 323-329 [PMID: 14528202 DOI: 10.1067/S0016-5107(03)00002-6]

21 **Chung SS**, Lau JY, Sung JJ, Chan AC, Lai CW, Ng EK, Chan FK, Yung MY, Li AK. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ* 1997; **314**: 1307-1311 [PMID: 9158465 DOI: 10.1136/bmj.314.7090.1307]

22 **García-Iglesias P**, Villoria A, Suarez D, Brullet E, Gallach M, Feu F, Gisbert JP, Barkun A, Calvet X. Meta-analysis: predictors of rebleeding after endoscopic treatment for bleeding peptic ulcer. *Aliment Pharmacol Ther* 2011; **34**: 888-900 [PMID: 21899582 DOI: 10.1111/j.1365-2036.2011.04830.x]

23 **Lin LF,** Siauw CP, Ho KS, [Tung JN](http://www.ncbi.nlm.nih.gov/pubmed/?term=Tung%20JN%5BAuthor%5D&cauthor=true&cauthor_uid=15648283). Hemoclip treatment for post-endoscopic sphincterotomy bleeding. *J Chin Med Assoc* 2004; **67**: 496-499 [PMID: 15648283]

24 **Sherman S**, Hawes RH, Nisi R, Lehman GA. Endoscopic sphincterotomy-induced hemorrhage: treatment with multipolar electrocoagulation. *Gastrointest Endosc* 1992; **38**: 123-126 [PMID: 1568606 DOI: 10.1016/S0016-5107(92)70375-7]

25 **Oviedo JA**, Barrison A, Lichtenstein DR. Endoscopic argon plasma coagulation for refractory postsphincterotomy bleeding: report of two cases. *Gastrointest Endosc* 2003; **58**: 148-151 [PMID: 12838247 DOI: 10.1067/mge.2003.320]

26 **Kuran S**, Parlak E, Oguz D, Cicek B, Disibeyaz S, Sahin B. Endoscopic sphincterotomy-induced hemorrhage: treatment with heat probe. *Gastrointest Endosc* 2006; **63**: 506-511 [PMID: 16500411 DOI: 10.1016/j.gie.2005.09.039]

27 **Katsinelos P**, Kountouras J, Chatzimavroudis G, Zavos C, Fasoulas K, Katsinelos T, Pilpilidis I, Paroutoglou G. Endoscopic hemostasis using monopolar coagulation for postendoscopic sphincterotomy bleeding refractory to injection treatment. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 84-88 [PMID: 20393333 DOI: 10.1097/SLE.0b013e3181d76ace]

**P-Reviewer:** Kozarek R **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Table 1 The 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 (× 103/μL) | 8.1 (5.6-10.0) | 8.1(6.0-10.7) | 0.673 |
|  Platelet count (× 103/μL) | 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) | 5.5 (2.2-7.3) | 5.1 ( 2.0-10.0) | 0.008 |
|  ESRD | 3 (8.6) | 10 (7.9) | 1.000 |
|  Decompensated liver cirrhosis | 4 (11.4 %) | 4 (3.2) | 0.069 |
|  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.

**Table 2 The 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 therapy1 | 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 |

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

**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 level1 |  |  |  |  |  |  |
| ≤ 10 | 1 |  |  | 1 |  |  |
| > 10 | 4.70 | 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 |  |  |  |

1A 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.