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Risk factor of bleeding after endoscopic sphincterotomy in average risk patients

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Abstract

Background For therapeutic endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy (ES) is necessary but it can lead to complications such as bleeding. Thus, we investigated the risk factors of post-ES bleeding in average risk patients.

Methods We retrospectively reviewed the medical records of patients who had been treated for ERCP between April 2006 and March 2013. The length of the ES incision was defined as minimal (up to proximal hooding fold), medium (between minimal and full length), and full (up to superior margin of sphincter opening). Exclusion criteria were as follows: if performed precut sphincterotomy or balloon dilatation, patients having altered anatomy or anticoagulant medications.

Results A total of 3620 patients underwent ERCP and 1121 patients who underwent biliary ES were enrolled. Post-ES bleeding occurred in 108 of 1121 patients (9.6%) and mostly minor bleeding (94 patients, 87%). Length of ES was the only risk factor for post-ES bleeding in multivariate analysis. Complete hemostasis was achieved by endoscopic modalities and no serious complication developed after hemostasis.

Conclusions In average risk patients, length of ES was independent risk factor for post-ES bleeding and endoscopic hemostasis was safe and effective.

Keywords Endoscopic retrograde cholangiopancreatography · Endoscopic sphincterotomy · Bleeding

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic technique widely used for diagnosing and treating various diseases of the biliary and pancreatic systems. However, magnetic resonance cholangiopancreatography, which is known to be as accurate as ERCP while being non-invasive, is now often used for diagnosis [1], while ERCP is usually performed for treatment purposes. In order to perform therapeutic ERCP, an endoscopic sphincterotomy (ES) needs to be performed as well, but this procedure can lead to complications such as acute pancreatitis, cholangitis, perforation, or bleeding [2]. Among these complications, post-ES bleeding occurs in 1–15% of patients, and although the bleeding is usually resolved by spontaneous hemostasis, the patient sometimes requires blood transfusion, endoscopic hemostasis, angiographic embolization, or surgery [3]. Several studies have already suggested that the risk factors include needle-knife sphincterotomy, periampullary diverticulum, coagulopathy, use of anticoagulants, and cholangitis. However, the relevance of these risk factors is still a matter of debate [4, 5]. Hence, the retrospective study reported herein aimed to identify further risk factors for only post-ES bleeding, except balloon dilatation or precut sphincterotomy.

Materials and methods

Patients

The present study considered a total of 3620 patients who underwent ERCP at the Daegu Catholic University Medical Center in the period between April 2006 and March 2014. The exclusion criteria for this retrospective study were the following: biliary drainage without ES, endoscopic papillary balloon dilatation, needle-knife infundibulotomy, pancreatic sphincterotomy, selective cannulation failure, altered

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anatomy such as post-gastrectomy state, biliary or pancreatic manometry, and minor papilla cannulation. Informed consent was obtained from each patient before ERCP (Fig. 1).

ERCP and biliary sphincterotomy

ERCP and biliary ES were performed by two experienced endoscopists (Ho Gak Kim, Jimin Han), who had performed at least 300 ERCPs per year for at least 10 years. ERCP was performed using two types of duodenoscope: JF-260V and TJF-260V (Olympus Optical, Tokyo, Japan). Local anesthesia of the oral cavity was induced using 10% lidocaine spray, and patients were sedated using intravenous midazolam and meperidine. Following the selective cannulation of the biliary duct using a hydrophilic guidewire, ES was performed in the 11–12 o'clock direction using a standard pull-type papillotome. The electrosurgical unit used during the operation was the VIO 300D (ERBE, Tübingen, Germany) set to the Endocut I mode (effect 2, output limit 155 W). The length of the ES incision was defined as minimal, if the incision was made from the papillary orifice to the proximal hooding fold; medium, if the incision was made from the papillary orifice to the midpoint between the proximal hooding fold and the superior margin of the sphincter opening; and full, if the incision was made from the papillary orifice up to the superior margin of the sphincter opening (Fig. 2).

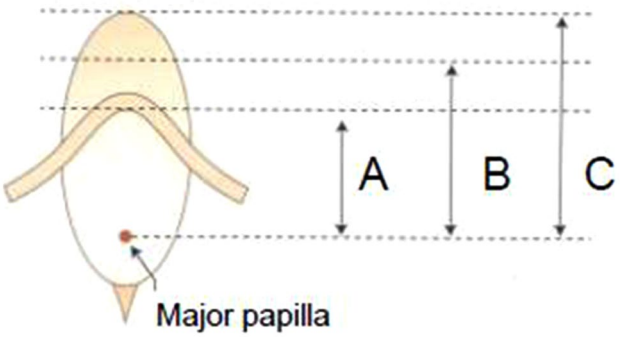

Fig. 2 The length of endoscopic sphincterotomy incision. (A) Minimal incision; (B) medium incision; (C) full incision

Post-ES bleeding

Post-ES bleeding was defined as immediate, if the onset of bleeding occurred during the ES; delayed, if the bleeding was not evident during the ES, but later manifested as melena or hematemesis, associated with a drop in hemoglobin levels. The severity of the bleeding was graded as mild, if there was only clinical or endoscopic evidence of bleeding, and no blood transfusion was required; moderate, if there was endoscopic evidence of bleeding,

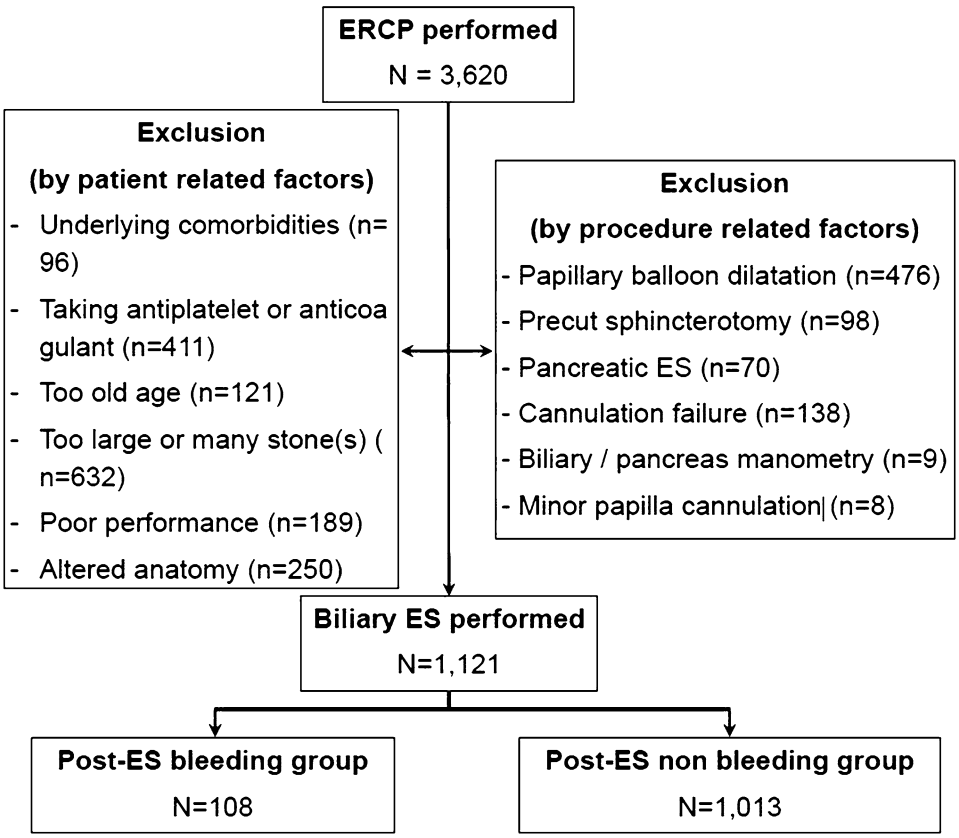

Fig. 1 A total number of 3620 ERCP cases were performed and 1121 patients underwent biliary ES. Post-ES bleeding was developed in 108 patients

requiring endoscopic hemostasis and blood transfusion of 4 units or less; and severe, if there was significant bleeding, requiring surgery or radiological embolization for control of bleeding, or requiring blood transfusion of 5 units or more [6].

Endoscopic hemostasis

When oozing bleeding was observed, endoscopic hemostasis was performed if spontaneous hemostasis did not occur, according to the surgeon's judgment. Endoscopic hemostasis was performed in all cases where there was pulsating or spurting bleeding, or if the bleeding vessel was exposed. The procedure for hemostasis involved bipolar electrocautery using a gold probe (Boston Scientific, Natick, mass), or injecting a mixed solution composed of 9 cc of 3% sodium chloride solution and 0.5 cc of 1:10,000 epinephrine solution. A combination of the two above-mentioned methods was also used where deemed necessary by the surgeon. If endoscopic hemostasis was not achieved, angioembolization and surgery were considered.

Use of antiplatelet or anticoagulation agents and underlying disease

If the patient was taking an antiplatelet agent such as aspirin, clopidogrel, or ticlopidine, ES was performed after discontinuing the relevant medication for 7 days, and upon consultation with a cardiologist or neurologist. The next day after ES, antiplatelet agents were taken again if there is no evidence of bleeding such as decreased hemoglobin, hypotension, tachycardia, melena, or hematochezia. For patients using an anticoagulation agent such as warfarin or heparin, an actual ES was not performed, and the surgical procedure was limited to inserting a drainage catheter.

Furthermore, the procedure was limited to drainage catheter insertion also in the following cases: patients undergoing hemodialysis for chronic kidney disease (CKD); patients with a platelet count of less than 100,000/mm^3; and patients with a prothrombin time (PT) or activated partial thromboplastin time (aPTT) of at least 1 s, or an international normalized ratio (INR) prolongation of at least 1.2.

Statistical analysis

Continuous variables, such as patient age and laboratory findings, were analyzed by the independent Student's t test. Categorical variables, such as indication for ES, use of an antiplatelet drug, presence of periampullary diverticulum, previous ES history, and length of ES incision were analyzed by the chi-squared test. The potential risk factors for ES-induced bleeding were examined by univariate and multivariate analysis, and evaluated by odds ratio with 95% confidence interval using a logistic regression method. A $p < 0.05$ was considered statically significant. Statistical analysis was performed using the statistical program SPSS v.15.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the patients

ERCP was performed in a total of 3620 cases. Many of these cases were excluded from the present study based on the following criteria: plastic stent or biliary drainage catheter insertion without ES ($n = 1650$), endoscopic papillary balloon dilatation ($n = 476$), precut sphincterotomy ($n = 98$), pancreatic sphincterotomy ($n = 70$), selective cannulation failure ($n = 138$), altered anatomy such as that produced by subtotal gastrectomy ($n = 50$), biliary or pancreatic manometry ($n = 9$), and minor papilla cannulation ($n = 8$). A total of 1121 patients who underwent biliary ES were included in the study. No post-ES bleeding was observed in 1013 patients (90.4%, non-bleeding group), while post-ES bleeding was observed in 108 patients (9.6%, bleeding group). In both groups of patients, ES was performed most frequently as treatment for biliary stone (76.9% and 70.7% for the bleeding and the non-bleeding group, respectively). The impacted stone at ampulla was more common in bleeding group (15.7% vs. 4.1%) and the difference was significant statically ($p = 0.048$). There were no significant differences between the two groups with respect to baseline characteristics such as the presence of a periampullary diverticulum, underlying disease, or laboratory findings (Table 1).

Post-ES bleeding

Out of the 108 patients who had post-ES bleeding, 88.0% ($n = 95$) had immediate bleeding, while 12.0% ($n = 13$) had delayed bleeding. Additionally, 87.0% ($n = 94$) had mild post-ES bleeding, while 13.0% ($n = 14$) had moderate post-ES bleeding. There were no events of severe post-ES bleeding (Table 2).

Endoscopic hemostasis

Out of the 108 patients who experienced post-ES bleeding, 97 patients required endoscopic hemostasis. All of the 97 patients achieved complete hemostasis following the endoscopic hemostasis procedure, and there were no patients who required angiographic embolization or surgery. Specifically, 50.9% ($n = 55$) of the patients achieved hemostasis solely by electrocautery, and 38.9% ($n = 42$) of the patients required both electrocautery and hypertonic

Table 1 Baseline characteristics of the patients

	Bleeding group ($n=108$)	Non-bleeding group ($n=1013$)	P value
Age (years)	66.6 ± 15.1	68.0 ± 14.1	0.980
Male, *n* (%)	67 (62.0)	548 (54.1)	0.127
Liver cirrhosis, *n* (%)	4 (3.7)	36 (3.6)	0.790
Hemodialysis, *n* (%)	2 (1.8)	13 (1.3)	0.842
Antiplatelet agent, *n* (%)	10 (9.2)	101 (9.9)	0.921
Thrombocytopenia, *n* (%)	10 (9.2)	55 (5.4)	0.105
Prolonged PT/aPTT, *n* (%)	11 (10.1)	128 (12.6)	0.541
Total bilirubin, *mg/dl*	6.5 (1.1–15.8)	5.4 (2.3–17.9)	0.117
Periampullary diverticulum, *n* (%)	37 (34.2)	312 (30.7)	0.110
Biliary stone, *n* (%)	83 (76.9)	716 (70.7)	0.105
Malignant obstruction, *n* (%)	16 (14.8)	159 (15.7)	0.360
Benign stricture, *n* (%)	7 (6.5)	87 (8.6)	0.705
Others, *n* (%)	6 (5.6)	51 (5.0)	0.880
Impacted stone at ampulla, *n* (%)	17 (15.7)	42 (4.1)	0.048
Length of ES, *n* (%)			
Minimal length	19 (17.6)	577 (57.1)	< 0.001
Medium length	52 (48.1)	294 (29.0)	0.004
Full length	37 (34.3)	142 (13.9)	< 0.001

Ages are expressed as the mean ± standard deviation

Total bilirubin is expressed as range, from minimum value to maximum value

PT prothrombin time, *aPTT* activated partial thromboplastin time

Others includes bile sludge, preoperative drainage such as Mirizzi syndrome or other hepatobiliary disease

Table 2 Classification of post-ES bleeding and its severity

	n (%)
Onset of post-ES bleeding	
Immediate bleeding	95 (88.0)
Delayed bleeding	13 (12.0)
Severity of post-ES bleeding	
Mild degree bleeding	94 (87.0)
Moderate degree bleeding	14 (13.0)
Severe degree bleeding	0 (0.0)

Table 3 Classification of hemostasis and clinical outcome

Hemostasis	*n* (%)
Electrocautery	55 (50.9)
Electrocautery + hypertonic saline injection	42 (38.9)
Observation (no hemostasis)	11 (10.2)
Clinical outcome	
Complete hemostasis	108 (100)
Re-bleeding	2 (1.8)

saline injection. The remaining 10.2% ($n=11$) of the patients achieved spontaneous hemostasis, and thus did not require endoscopic hemostasis (Table 3).

Clinical outcome and complications after hemostasis

None of the 11 patients who had spontaneous hemostasis experienced re-bleeding. Out of the 97 patients who underwent endoscopic hemostasis, 2 patients experienced re-bleeding. However, both patients achieved hemostasis by means of a secondary endoscopic hemostasis, and there was no further re-bleeding or requirement for additional management such as embolization or surgery (Table 3).

After endoscopic hemostasis was performed, 6 patients (6.2% of the patients who required endoscopic hemostasis) developed pancreatitis. However, all of these were cases of mild pancreatitis that improved with 2–3 days of fasting. And hyperamylasemia with or without hyperlipasemia (elevated less than 3 times) was observed in 15 patients. Unlikely patients with pancreatitis, they did not suffer from abdominal pain and the normal findings were seen in later blood test. Additionally, there were no events of perforation, cholangitis, or cholecystitis (Table 4).

Risk factors related to post-ES bleeding

According to the univariate analysis, the impacted stone at ampulla and longer ES incision were associated with a higher risk of post-ES bleeding. The presence of a

Table 4 Complication after endoscopic hemostasis

Complications	*n* (%)
Pancreatitis	6 (6.2)
Hyperamylasemia (and/or lipasemia)	15 (15.5)
Perforation	0 (0.0)
Cholangitis	0 (0.0)
Cholecystitis	0 (0.0)

Table 5 Risk factors related post-ES bleeding in univariate and multivariate analyses

Variable	OR	95% CI	*p* value
Univariate			
Impacted stone			
No	1		
Yes	3.21	1.50–6.06	0.033
Length of ES			
Minimal length	1		
Medium length	20.61	12.04–35.27	< 0.001
Full length	83.86	7.18–472.79	< 0.001
Multivariate			
Impacted stone			
No	1		
Yes	3.51	0.93–9.11	0.213
Length of ES			
Minimal length	1		
Medium length	10.97	5.90–24.87	0.011
Full length	68.27	8.74–422.14	< 0.001

OR odds ratio, *CI* confidence interval

periampullary diverticulum showed no relationship. However, when the factors were investigated by a multivariate analysis, only longer ES incision was found to be associated with a higher risk of post-ES bleeding (Table 5).

Discussion

Since it was first introduced in 1974, ES has been used extensively, especially to facilitate the removal of bile duct stones [7]. Indeed, the present study also found that biliary stone was the most common indication for ES. The rate of post-ES complications has been decreasing as a result of the recent advancements in endoscopic equipment and increasing experience in the field. Nevertheless, post-ES bleeding is a clinically important complication [8].

Although there are some reports that it is more common for patients to experience bleeding immediately following the ES procedure (immediate bleeding) rather than 24 h after the procedure (delayed bleeding) [6, 9], most prospective studies report a higher incidence of delayed bleeding [10, 11]. In the present study, 88% of the patients who experienced post-ES bleeding had immediate bleeding. This finding may be influenced by the strict selection criteria for patients undergoing ES. This study not only excluded CKD patients receiving hemodialysis, patients who had a platelet count of less than 100,000/mm^3, and patients who had severe coagulopathy according to the PT/aPTT test, but also only included patients who had stopped taking antiplatelet or anticoagulation agents that can affect hemostasis. This may be the reason why the present study reported less clinically significant bleeding after 24 h.

As with other forms of gastrointestinal bleeding, there are various methods of performing endoscopic hemostasis for post-ES bleeding. Tsou YK et al. reported that single therapy using only epinephrine solution injection is as effective for treating post-ES bleeding as combination therapy using thermotherapy and an epinephrine solution [12]. Endoscopic hemoclip treatment can also be used as a mechanical method, but this requires special precautions. This is because there is limited vision when using a hemoclip with a duodenoscope during active bleeding, and pancreatitis can occur if the pancreatic duct is accidentally clamped [13]. Other researchers described the balloon tamponade method and the band-ligation method using a balloon catheter, but the efficacy of these methods has not been fully proven yet [14, 15]. The fact that application of electrocautery current is more difficult than injection therapy represents the biggest drawback of the thermal method. However, when a visible vessel or specific bleeding point is exposed, electrocautery can be an effective hemostasis method [16]. For the patients included in this study, bipolar electrocautery was used instead of a heat probe when performing hemostasis. In contrast to the heat probe method, which uses monopolar electrocautery or direct heat transfer, bipolar electrocautery is known to desiccate the target tissue, decreasing the electrical conductivity and minimizing the depth and breadth of tissue injury [17].

To date, several studies have reported hemodialysis, coagulopathy, thrombocytopenia, periampullary diverticulum, biliary stone, previous sphincterotomy, and impacted stone at ampulla as risk factors for post-ES bleeding [5, 6, 18]. Additionally, it is known that altered anatomy, such as that produced by subtotal gastrectomy, can constitute a risk factor for post-ES bleeding [3]. In the present study, most of the risk factors suggested by previous research were accounted for by the exclusion criteria, and thus were not analyzed. Furthermore, the European Society of Gastrointestinal Endoscopy and the American Society for Gastrointestinal Endoscopy suggest that clopidogrel and prasugrel should be discontinued before ES, while aspirin can be continued [19, 20]. However, upon consultation with a cardiologist

or neurologist, all related medication was discontinued for 7 days before the ES procedure for all the patients involved in the present study. Finally, it has been reported that the level of experience of the endoscopist can be a factor for post-ES complications including bleeding [10]. Nonetheless, as the endoscopists who treated the patients involved in this study have more than 10 years of experience performing at least 300 ERCPs per year, this aspect can be excluded from the potential risk factors.

As a result of minimizing the endoscopist- and patient-related risk factors (underlying disease and condition) and focusing instead on the procedure-related risk factors, the length of the ES incision were confirmed as independent risk factors for post-ES bleeding. And even if there was bleeding event after longer ES, it could be treat endoscopically without severe complications. This conclusion can be interpreted in two ways. At first, if all possible risk factors are excluded as described above, full length of ES can be considered under careful observation. The next, minimal length of ES was the way of minimal post-ES bleeding in the patients with no risk factors of post-ES bleeding.

The present study has four limitations. First, this was a retrospective study, and thus selection bias may have occurred. However, the medical center involved in the study constructed its own database containing data from the past 20 years, during which time the patients who received ERCP were followed consistently. Although this is a retrospective study, selection bias is expected to be minimal because the present study is also based on the extensive database maintained by the medical center. Second, compared to other studies, there were no recorded failures of the endoscopic hemostasis procedure or severe bleeding such as surgery/radiological embolization, and the incidence of endoscopic hemostasis-related complications or re-bleeding was low. This is because the inclusion criteria were stricter than in other studies, adding support to the evidence that the length of the ES incision is a risk factor for post-ES bleeding. Third, severity of bleeding can be subjective and oozing type bleeding can sometimes stop spontaneously without clinical signs. That is why the incidence of post-ES bleeding is relatively higher than other studies (9.6%). Furthermore, ES was not performed according to the same protocol and the length was estimated based on image and medical records. Thus, severity of bleeding and the length of ES are subjective and they may be having some kind of bias. For this reason, well-designed randomized prospective study may be needed in the same patient group. At last, the number of patients with post-ES bleeding was relatively small, so if a sufficient number of patients are enrolled, other risk factors of post-ES bleeding can be added such as cholangitis, jaundice, and impacted stone.

The present study investigated the risk factors for post-ES bleeding while eliminating or minimizing the influence of risk factors already reported by other studies. The results revealed that the length of the ES incision is the most important factor. Therefore, endoscopists who perform ERCP should aim to restrict the ES incision to the minimum required length in order to prevent post-ES bleeding. If the post-ES bleeding occurs, endoscopic hemostasis should be considered at first and it is an effective and safe enough.

Compliance with ethical standards

Disclosures Sang Soo Bae, Dong Wook Lee, Jimin Han, and Ho Gak Kim have no conflicts of interest or financial ties to disclosure.

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