Digestive Endoscopy 2014; **26**: 737–744 doi: 10.1111/den.12271

Original Article

Effect of sustained use of platelet aggregation inhibitors on post-endoscopic sphincterotomy bleeding

Min Geun Lee,[1,4] Jaihwan Kim,[1,3] Sang Hyub Lee,[1,2] Ban Seok Lee,[1,2] Seung June Lee,[1,3] Yoon Suk Lee,[1,3] Byung Hyo Cha,[5] Jin-Hyeok Hwang,[1,3] Ji Kon Ryu[1,2] and Yong-Tae Kim[1,2]

[1]*Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine,* [2]*Department of Internal Medicine, Seoul National University Hospital, Seoul,* [3]*Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si,* [4]*Department of Internal Medicine, Hanmaeum Hospital and* [5]*Department of Internal Medicine, Halla Hospital, Jeju-si, Korea*

Background and Aim: The effect of platelet aggregation inhibitors (PAI) on post-endoscopic sphincterotomy (ES) bleeding in patients who cannot discontinue PAI for sufficient time in urgent conditions has not been identified. The present study analyzed the effect of sustained use of PAI on post-procedural bleeding in patients undergoing ES.

Methods: A total of 762 patients were grouped into one of the following groups: no-PAI group (n = 601), continuation group (n = 132), and withdrawal group (n = 29). The continuation group included sustained PAI therapy (sustained user, n = 49) or those in whom therapy was interrupted <7 days prior to ES (non-sustained user, n = 83). The primary outcome was defined as the incidence, type, and severity of post-ES bleeding among groups.

Results: There were no significant differences between incidence, type, or severity of post-ES bleeding in the three groups. Among 132 patients with continued use of PAI, there was no significant difference regarding incidence and severity of bleeding according to sustained or non-sustained use (P = 0.071 and P = 0.086, respectively). However, post-ES delayed bleeding was more frequent in sustained PAI users than in non-sustained users (7/49, 14.3% *vs* 2/83, 2.4%) and was significantly associated with sustained PAI therapy in the continuation group (P = 0.013).

Conclusion: Sustained use of PAI without interruption until ES might increase the risk of delayed bleeding.

Key words: acetylsalicylic acid, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy (ES), gastrointestinal hemorrhage, platelet aggregation inhibitor

INTRODUCTION

SINCE THE ADVENT of endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) in 1974,[1] ES has become the most commonly carried out standard procedure for the clearance of stones from the bile duct,[2,3] for the placement of stents through malignant or benign biliary strictures and for a wide variety of biliary and pancreatic diseases.[4] However, ES is associated with serious procedure-related complications such as bleeding, pancreatitis, perforation and recurrent infection of the bile duct.[5]

Corresponding: Sang H. Lee, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea. Email: gidoctor@snuh.org
Min Geun Lee and Jaihwan Kim contributed equally to this work as first authors.
Received 1 November 2013; accepted 10 February 2014.

Platelet aggregation inhibitors (PAI), acetylsalicylic acid (ASA; aspirin) and clopidogrel, in particular, are widely used for both primary and secondary prevention of cardiovascular and cerebrovascular diseases. It is well established that ASA is associated with a risk of upper gastrointestinal bleeding, which is even further increased when combined with clopidogrel.[6,7]

The overall risk of post-sphincterotomy bleeding is 0.3–12.1%, with a mortality rate of approximately 0.1%.[8–12] The presence of pre-ERCP cholangitis, coagulation disorders, the use of anticoagulation agents within 3 days after ES, and bleeding during the procedure are known risk factors for post-ES bleeding, but the significance of these factors is still under debate.[8–10,13]

So far, a few studies have assessed the relative risk of PAI use in patients undergoing ES.[9,10,14] For ES, recently published guidelines recommended to continue ASA and withhold clopidogrel.[15] However, this was a low-grade recommendation without results of large-scale trials, and there was a wide variation in practice regarding the

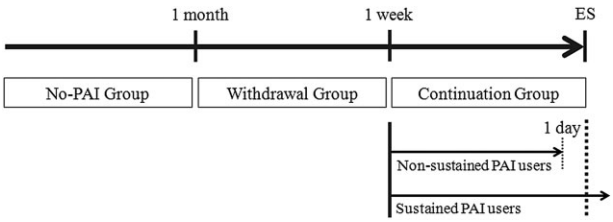

Figure 1 Visual presentation of the present study design. ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

discontinuation of PAI. Also, there are insufficient data concerning the risk of bleeding and procedural benefits after ES and on the effects of PAI on post-ES bleeding, although significant cases of therapeutic ERCP are done without interruption of PAI for a sufficient time as a result of emergency situations, such as septic cholangitis, or in clinical cases related to a high risk of thromboembolism.

We thus undertook the present study to evaluate the effect of PAI on post-procedural bleeding in patients undergoing ES in the above clinical situations.

METHODS

Patients

A RETROSPECTIVE AUDIT was conducted on patients who had undergone ERCP at Seoul National University Bundang Hospital from September 2008 to February 2012, inclusive. Among 1353 patients, the following subjects were excluded. Patients who underwent pancreatic sphincterotomy and ES combined with endoscopic papillary balloon dilatation, with ongoing use of anticoagulants, such as warfarin or heparin, non-steroidal anti-inflammatory drugs (NSAIDs), or selective serotonin reuptake inhibitors or with coagulopathy. Coagulopathy was defined as a platelet count ≤100 000/mL, international normalized ratio >1.5, and partial thromboplastin time above the normal value for the institution. Therefore, a total of 762 patients who had undergone ES were included in this analysis. Various patient- and procedure-related parameters were recorded during ERCP. Full details of the diagnosis, procedure, and complications were recorded in a database. The medical records (electronic charts) of these patients were meticulously reviewed. Participants were grouped into one of the following groups: no-PAI group, continuation group, and withdrawal group. Patients who had sustained PAI therapy or had it interrupted <7 days before ES were classified into the continuation group, and those who had never used PAI or had it discontinued ≥30 days prior to ES were classified into the no-PAI group. Others were classified into the withdrawal group (Figs 1,2).

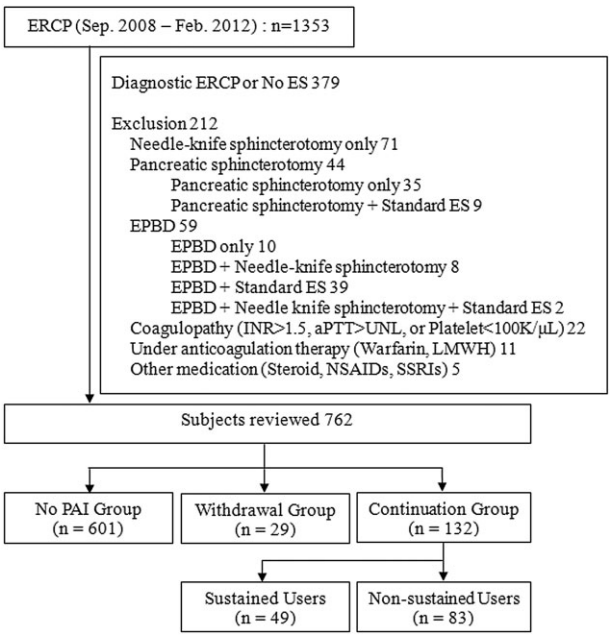

Figure 2 A total of 762 patients undergoing endoscopic sphincterotomy (ES) were reviewed retrospectively. EPBD, endoscopic papillary balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography; INR, international normalized ratio; LMWH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs; PAI, platelet aggregation inhibitors; PTT, partial thromboplastin time; SSRIs, selective serotonin re-uptake inhibitors; UNL, upper normal limit.

PAI were defined as drugs that decrease platelet aggregation or inhibit thrombus formation as follows: ASA, clopidogrel or ticlopidine, cilostazol, and sarpogrelate. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

Procedures

Patients were given a topical throat spray with 10% lidocaine and were sedated with i.v. midazolam and pethidine hydrochloride. ERCP and its associated procedures were done with side-viewing endoscopes (JF-240, TJF-240, JF-260 and TJF-260; Olympus, Tokyo, Japan). All endoscopists had more than 5 years of experience in carrying out therapeutic ERCP. Sphincterotomy was made in the 11–12 o'clock direction using a standard pull-type papillotome (Clever-Cut; Olympus, Tokyo, Japan). If standard sphincterotomy failed, precut was carried out using a triple-lumen needle-type papillotome (Microknife XL; Boston Scientific Co., Marlborough, MA, USA), followed by additional ES. The electrosurgical unit (ICC 200; ERBE, Tübingen, Germany) was used at approximately 40 W/s of blended current. In

cases of consistent bleeding (either active oozing or arterial spurting observed on endoscopy which did not stop spontaneously after 2–3 min) endoscopic hemostasis was carried out. ERCP was completed when bleeding was no longer evident for a minimum of 5 min during endoscopic observation.

Outcome measurements and definition of events

The primary outcome of the current study was defined as the incidence, type and severity of post-ES bleeding according to the use of PAI. In addition, in the continuation group, measurement of outcomes was carried out according to the sustained use of PAI on post-ES bleeding in clinical situations when PAI could not be discontinued for a sufficient amount of time.

Post-ES bleeding was defined as an episode of any of the following: clinical evidence of bleeding, such as melena, hematemesis or hematochezia, or a decrease in hemoglobin of >2 g/dL from baseline after the procedure[16] irrespective of clinical evidence of bleeding or requirement of transfusion. Bleeding following the procedure was presumed to result from ES unless another cause was documented. The type of post-sphincterotomy bleeding was classified as early and delayed. Early bleeding was defined as a bleeding episode within 24 h after ES, and delayed bleeding was defined as bleeding for >24 h after ES but not evident at the end of the procedure.[16] Patients who did not experience bleeding after the procedure with spontaneous hemostasis or endoscopic hemostasis were not included in the present study.

The severity of post-ES bleeding was graded based on the modified grading system proposed by Cotton and Williams.[17] Mild bleeding was defined as a hemoglobin drop of <3 g/dL and no need for blood transfusion, moderate bleeding as a hemoglobin drop of >3 g/dL or transfusion (≤4 units), and severe bleeding as transfusion of ≥5 units in those requiring intervention (surgery or radiological embolization).

Evaluation of demographic and clinical variables according to clinical outcomes

The comorbidity index developed by Charlson *et al.*[18] is a validated method of classifying comorbidity to predict short- and long-term mortality using medical records. Repeated cannulation was defined as the need for more than six attempts before achieving successful deep cannulation of the common bile duct.[19] Full-length incision was accomplished by extending the incision up to the major horizontal fold crossing the intramural portion of the bile duct or superior margin of the papilla bulge.[16]

Endoscopic hemostasis during ERCP was carried out for sustained endoscopic venous oozing with injection therapies, balloon tamponade, and application of coagulation current using sphincterotomes.

To investigate potential risk factors that influence post-ES bleeding, the following variables were analyzed; age (<65 or ≥65 years), sex, Charlson comorbidity index (CCI) score, indication for ES (acute cholangitis before the procedure or choledocholithiasis), existence of periampullary diverticulum, precutting with a needle knife, repeated cannulation, length of ES, hemostatic procedure during ERCP, combined PAI therapy, and status of PAI therapy (no-PAI, continuation, or withdrawal).

Statistical analysis

Demographic and clinical characteristics were compared among the three groups, between the continuation groups (sustained versus non-sustained PAI users) and between those with or without bleeding after ES. Categorical variables were compared using the χ^2-test or Fisher's exact test, and were compared using Student's *t*-test and one-way analysis of variance (ANOVA). Binary logistic regression with step-wise selection was used to identify independent variables associated with post-ES bleeding. A P-value <0.05 was considered significant. All analyses were carried out with the Statistical Package for the Social Sciences, version 18.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Patient groups

DURING THE STUDY period, a total of 1353 ERCP were carried out at our center; 762 of these involved ES. Among a total of 762 subjects, 161 (21.1%) took PAI therapy. ASA users comprised the biggest proportion, 62.1%, followed by 18.6% of dual PAI users with ASA and clopidogrel.

Patients were distributed into three groups based on PAI intake: patients who never used PAI ($n = 601$), patients whose PAI was withdrawn ($n = 29$), and those on continuous PAI therapy ($n = 132$). The overall characteristics of patients according to PAI use are summarized in Table 1.

Outcome measurements in overall patients

Of the 762 ES included, there were 79 cases (10.4%) of post-ES bleeding recorded (27 early, 52 delayed; mean, 3.22 ± 2.48 days). Thirteen of the bleeding episodes occurred in the continuation group (9.8%), three in the withdrawal group (10.3%), and 63 in the no-PAI group (10.5%). There were no significant differences between incidences of post-ERCP bleeding ($P = 0.977$), and there were no significant differences in type and severity (Table 2). Among the

Table 1 Clinical characteristics of patients according to the use of PAI

	No-PAI group (*n* = 601)	Withdrawal group (*n* = 29)	Continuation group (*n* = 132)	*P*-value
Age, years, mean (SD)	60.8 (16.1)	74.9 (10.7)	72.3 (9.7)	<0.001
Age ≥65 years, *n* (%)	281 (46.8)	26 (89.7)	109 (82.6)	<0.001
Male sex, *n* (%)	329 (54.7)	19 (65.5)	82 (62.1)	0.182
CCI score, mean (SD)	2.6 (2.2)	4.3 (2.0)	4.4 (2.0)	<0.001
Cholangitis, *n* (%)	245 (40.8)	12 (41.4)	62 (47.0)	0.424
Choledocholithiasis, *n* (%)	284 (47.3)	18 (62.1)	75 (56.8)	0.053
Periampullary diverticulum, *n* (%)	121 (20.1)	6 (20.7)	30 (22.7)	0.800
Precut with needle knife, *n* (%)	45 (7.5)	1 (3.4)	15 (11.4)	0.217
Repeated cannulation, *n* (%)	71 (11.8)	4 (13.8)	25 (18.9)	0.089
Full length of ES, *n* (%)	170 (28.3)	6 (20.7)	27 (20.5)	0.138
Endoscopic hemostasis during ERCP, *n* (%)	17 (2.8)	2 (6.9)	3 (2.3)	0.359
Combined PAI therapy, *n* (%)		13 (44.8)	41 (31.1)	<0.001

CCI, Charlson comorbidity index; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

Table 2 Incidence, type and severity of post-ES bleeding among the three groups in the present study

	No-PAI group (*n* = 601)	Withdrawal group (*n* = 29)	Continuation group (*n* = 132)	*P*-value
Overall post-ES bleeding, *n* (%)	63 (10.5)	3 (10.3)	13 (9.8)	0.977
Time of bleeding event, days, median (range)	3.25 (1–11)	2.67 (1–4)	3.00 (1–7)	0.884
Type of bleeding, *n* (%)				0.998
Early	22 (3.7)	1 (3.4)	4 (3.0)	
Delayed	41 (6.8)	2 (6.9)	9 (6.8)	
Severity of bleeding, *n* (%)				0.490
Mild	48 (8.0)	2 (6.9)	10 (7.6)	
Moderate/severe	15 (2.5)	1 (3.4)	3 (2.3)	

ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

27 patients with early post-ES bleeding, 21 cases were classified as mild bleeding, two as moderate bleeding, and one as severe bleeding. Among the 52 patients with delayed post-ES bleeding (mean, 4.3 days; range, 2–11 days), 39 episodes were classified as mild bleeding, and 13 as moderate bleeding. Among the 27 patients with early post-ES bleeding, angiographic embolization was done in one subject to control severe bleeding. Five patients required blood transfusion; the patient with the most severe bleeding received a total of 9 units of packed red cells. No patient required surgery, and there was no mortality as a result of post-ES bleeding. Figure 3 shows no difference in incidence of post-ES bleeding in patients with actual bleeding events among the three groups ($P = 0.870$).

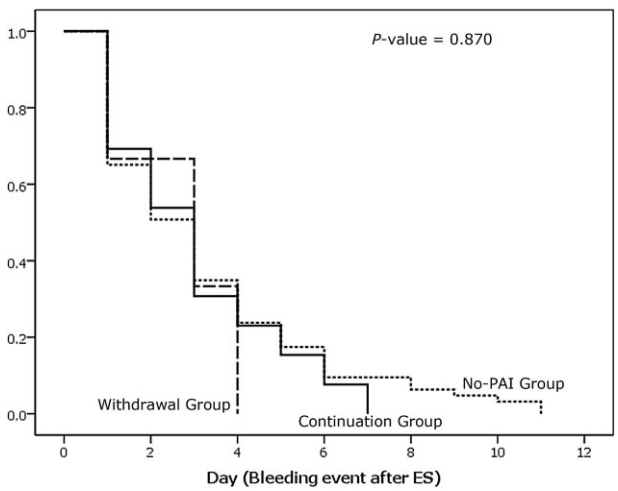

Figure 3 Kaplan–Meier plots in patients with bleeding events among the three groups (no. patients 79: no-PAI group 63/601, withdrawal group 3/29, and continuation group 13/132). ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

Outcome measurements in the continuation group

A total of 132 patients on sustained PAI therapy or who had it interrupted for <7 days prior to ES were included in the

Table 3 Clinical characteristics of the continuation group according to sustained or non-sustained use of PAI

	Sustained users (*n* = 49)	Non-sustained users (*n* = 83)	*P*-value
Age, years, mean (SD)	72.0 (11.1)	72.5 (8.8)	0.734
Age ≥65 years, *n* (%)	40 (81.6)	69 (83.1)	0.826
Male sex, *n* (%)	32 (65.3)	50 (60.2)	0.562
CCI score, mean (SD)	4.3 (2.2)	4.4 (1.9)	0.736
Cholangitis, *n* (%)	28 (57.1)	52 (62.7)	0.532
Choledocholithiasis, *n* (%)	28 (57.1)	47 (56.6)	0.954
Periampullary diverticulum, *n* (%)	20 (40.8)	29 (34.9)	0.500
Precut with needle knife, *n* (%)	6 (12.2)	12 (14.5)	0.720
Repeated cannulation, *n* (%)	5 (10.2)	10 (12.0)	0.747
Full length of ES, *n* (%)	3 (6.1)	3 (3.6)	0.504
Endoscopic hemostasis during ERCP, *n* (%)	1 (2.0)	2 (2.4)	0.891
Combined PAI therapy, *n* (%)	9 (18.4)	14 (16.9)	0.966

CCI, Charlson comorbidity index; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

Table 4 Incidence, type and severity of post-ES bleeding in the continuation group according to sustained or non-sustained use of PAI

	Sustained users (*n* = 49)	Non-sustained users (*n* = 83)	*P*-value
Overall post-ES bleeding, *n* (%)	8 (16.3)	5 (6.0)	0.071
Time of bleeding event, days, median (range)	3.6 (1–7)	2 (1–5)	0.162
Type of bleeding, *n* (%)			0.038
Early	1 (2.0)	3 (3.6)	
Delayed	7 (14.3)	2 (2.4)	
Severity of bleeding, *n* (%)			0.086
Mild	6 (12.2)	4 (4.8)	
Moderate/severe	2 (4.1)	1 (1.2)	

ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

analysis. Single ASA users made up the biggest proportion (86/132, 65.2%), followed by 13.6% of dual PAI users with ASA and clopidogrel. The incidence, type, and severity of post-ES bleeding were analyzed to evaluate the effect of sustained administration of PAI on post-ES bleeding. Baseline characteristics and procedure-related factors in sustained users ($n = 49$) versus non-sustained users ($n = 83$) of PAI are listed in Table 3. Causes of sustained use of PAI without interruption prior to ES were emergency therapeutic ERCP as a result of acute septic cholangitis ($n = 20$), high risk of thromboembolism ($n = 21$) or combined problems ($n = 8$). There was no significant difference regarding the bleeding rate and severity between sustained and non-sustained users ($P = 0.071$ and $P = 0.086$, respectively). However, the type of post-ES bleeding differed among the groups ($P = 0.038$). Seven cases of delayed bleed ing occurred in sustained users (14.3%), two in non-sustained users (2.4%), showing a relationship between delayed bleeding and PAI use (Table 4). There were no significant differences in bleeding incidences among single aspirin users (9/86, 10.5%), thienopyridine monotherapy (2/14, 14.3%), another PAI monotherapy (1/8, 12.5%), and prescription of multiple agents (1/24, 4.2%) ($P = 0.681$). Post-ES delayed bleeding was significantly associated with sustained PAI therapy in the continuation group ($P = 0.013$) (Table 5). However, univariate analysis failed to clarify any risk factors for early bleeding. We carried out subgroup analysis among the sustained PAI group (emergency ERCP group, $n = 28$ *vs* elective ERCP group, $n = 21$). There were no significant differences in basal characteristics except in CCI score (4.9 *vs* 3.5, $P = 0.034$) and in bleeding outcomes among groups (data not shown). There were no significant differences in post-ES bleeding rate in patients in the continuation group (sustained PAI *vs* non-sustained PAI group, $P = 0.120$) or in the sustained PAI group (elective ERCP *vs* emergency ERCP group, $P = 0.214$) (Figs 4,5).

Table 5 Risk factors for post-ES delayed bleeding in logistic regression analyses among the continuation group

	Post-ES delayed bleeding		*P*-value
	Yes (*n* = 9)	No (*n* = 123)	
Age, years, mean (SD)	68.2 (14.1)	72.6 (9.3)	0.381
Age ≥65 years (%)	6 (66.7)	103 (83.7)	0.190
Male sex, *n* (%)	7 (77.8)	75 (61.0)	0.482
CCI score, mean (SD)	3.9 (1.8)	4.4 (2.0)	0.469
Cholangitis, *n* (%)	5 (55.6)	75 (61.0)	0.738
Choledocholithiasis, *n* (%)	4 (44.4)	71 (57.7)	0.499
Periampullary diverticulum, *n* (%)	4 (44.4)	45 (36.6)	0.726
Precut with needle knife, *n* (%)	2 (22.2)	16 (13.0)	0.354
Repeated cannulation, *n* (%)	2 (22.2)	13 (10.6)	0.271
Full length of ES, *n* (%)	1 (11.1)	5 (4.1)	0.351
Endoscopic hemostasis during ERCP, *n* (%)	0	3 (2.4)	1.000
Combined PAI therapy, *n* (%)	0	24 (19.5)	0.364
Sustained use of PAI, *n* (%)	7 (77.8)	42 (34.1)	0.013

CCI, Charlson comorbidity index; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

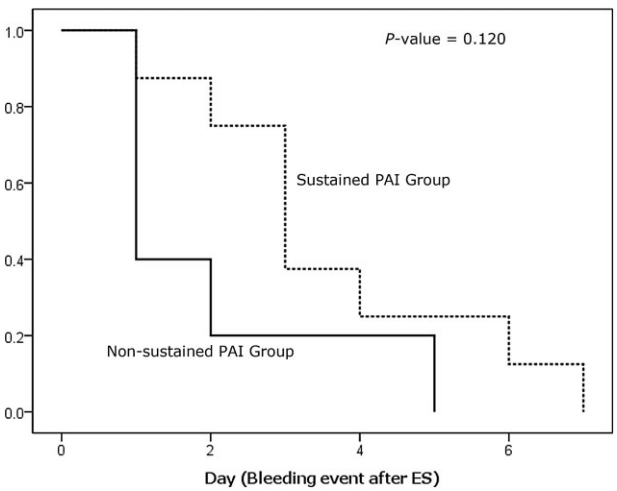

Figure 4 Kaplan–Meier plots in patients with bleeding events between two groups (no. patients 13: sustained group 8/49, non-sustained group 5/83). ES, endoscopic sphincterotomy; PAI, platelet aggregation inhibitors.

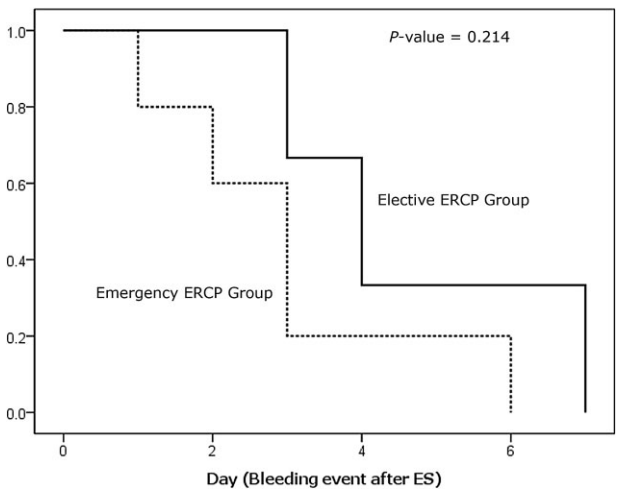

Figure 5 Kaplan–Meier plots in patients with bleeding events between the two groups (no. patients 8; emergency ERCP 5/28, elective ERCP group 3/21). ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy.

DISCUSSION

ENDOSCOPIC BILIARY SPHINCTEROTOMY was stratified as a high-risk procedure based on the risk of bleeding.[5] The use of PAI increases as the incidence of cardiovascular or cerebrovascular disease increases. Post-endoscopic procedure-related bleeding is a well-known complication of these agents.

A substantial number of cases of ERCP have been carried out without sufficient time for discontinuation of PAI in urgent conditions such as septic cholangitis or in patients with clinical indications for PAI because of a high risk of thromboembolism. However, there are few existing data about the specific effects of PAI on post-ES bleeding. Therefore, we analyzed whether the sustained intake of PAI is associated with the incidence, type and severity of post-ES bleeding. Our study showed that the sustained use of PAI increased post-ES delayed bleeding.

The American Society for Gastrointestinal Endoscopy indicates that, in the absence of a pre-existing bleeding dis-

order, endoscopic procedures may be carried out in patients taking ASA, and that clopidogrel should be stopped 7–10 days before carrying out a higher risk procedure.[15,20] However, this recommendation was based on low-level evidence without results from large-scale trials, with a lack of consensus among gastroenterologists regarding the management of these agents in the peri-endoscopic period.

The overall risk of post-ES bleeding in patients taking PAI is 2.1–10%.[9,10,14] In the current study, the incidence (9.8%, 13/132) of post-ES bleeding among continuous PAI users is higher than in most reported series because we included a drop of hemoglobin >2 g/dL from baseline without clinical evidence of bleeding.

We identified several studies that assessed post-ES bleeding in patients taking PAI. The first retrospective cohort study by Nelson and Freeman[10] showed that the major bleeding rate was 10% (5/50) in patients who had taken ASA or NSAIDs within 1 week of sphincterotomy. This was higher than in the control group (5.3%, 10/189), but the use of ASA was not an independent risk factor. Similarly, a study by Freeman *et al*.,[9] reported that clinically significant post-ES bleeding occurred in 2% (48/2347), regardless of the use of ASA or NSAIDs (2.1%, 6/292) during 3 days preceding the procedure. However, these studies only included the effect of ASA or NSAIDs on post-ES bleeding, and did not show the results regarding the type or severity of post-ES bleeding.

In contrast, Hui *et al*.,[14] reported that the use of ASA therapy (regardless of whether ASA was sustained or interrupted for 1 week before ES) significantly increased the incidence of post-ES bleeding (9.6%, 23/240) compared with the no-PAI group (3.9%, 22/564, $P = 0.01$) and increased the risk of post-ES delayed bleeding in the sustained or withdrawal group (6.7%, 16/240) compared with the no-PAI group (2.7%, 15/564, $P = 0.009$). However, these authors concluded that although ASA increased the risk of post-ES bleeding, withholding ASA for 1 week prior to ES did not decrease the risk of procedure-related bleeding.

Aspirin has definite effects on platelet aggregation through inhibition of cyclo-oxygenase-1 activity of prostaglandin[21] and prolongs bleeding time for as long as 48 h (1.2–2.0-fold) after ingestion.[6] Clopidogrel and ticlopidine, both of the thienopyridine family, primarily inhibit platelet aggregation by inhibiting ADP-induced activation of platelet fibrinogen.[22] They are known to be as effective as ASA in prolonging bleeding time.[23] This is the reason why the sustained use of PAI before the procedure increases the risk of post-ES bleeding. The higher rate of post-ES delayed bleeding in sustained PAI users suggests that it may be a better rationale to withhold PAI prior to ES, but this remains to be proven.

Our study has some limitations. The main limitation is that it is a retrospective review with data collected from a single center. As a result, we could not find differences in incidence, type and severity of post-ES bleeding among the three groups (no-PAI, withdrawal, and continuation groups). The second limitation is that no difference in incidences or severities of post-ES bleeding was found between two groups (sustained *vs* non-sustained users), but the groups were too small to find such a difference even if it exists, so the study is underpowered. However, the data in our study included an additional three PAI as well as clopidogrel, although of a small percentage, which is a more potent PAI than ASA and could be useful to endoscopists carrying out ERCP in urgent situations without discontinuation of PAI. Another limitation is that there is a possibility that the incidence of post-ES bleeding was higher than that in other reports because of the criteria as a drop in hemoglobin >2 g/dL from baseline after the procedure irrespective of clinical evidence of bleeding.

In conclusion, post-ES delayed bleeding may increase as a result of sustained PAI therapy prior to ES, so more meticulous treatment of bleeding during ES is warranted. Therefore, further attention should be paid to post-ES delayed bleeding in cases without interruption of PAI as a result of urgent conditions such as septic cholangitis or in patients with a high risk of thromboembolism.

ACKNOWLEDGMENT

WE WOULD LIKE to thank all the participating patients.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article. This study was not supported by any grant.

REFERENCES

1 Kawai K, Akasaka Y, Murakami K, Tada M, Kohli Y, Nakajima M. Endoscopic sphincterotomy of the ampulla of Vater. *Gastrointest. Endosc.* 1974; **20**: 148–51.
2 Cotton P, Chung S, Davis WZ, Gibson R, Ransohoff D, Strasberg S. Issues in cholecystectomy and management of duct stones. *Am. J. Gastroenterol.* 1994; **89**: S169–76.
3 Strasberg SM, Soper NJ. Management of choledocholithiasis in the laparoscopic era. *Gastroenterology* 1995; **109**: 320–22.
4 Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter-of-Oddi dysfunction. *N. Engl. J. Med.* 1989; **320**: 82–7.
5 Riemann J, Lux G, Förster P, Altendorf A. Long-term results after endoscopic papillotomy. *Endoscopy* 1983; **15**: 165–8.

6 Nakajima H, Takami H, Yamagata K, Kariya K, Tamai Y, Nara H. Aspirin effects on colonic mucosal bleeding. *Dis. Colon Rectum* 1997; **40**: 1484–8.
7 Fork FT, Lafolie P, Toth E, Lindgärde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers: A gastroscopic study. *Scand. J. Gastroenterol.* 2000; **35**: 464–9.
8 Leung JWC, Chan FKL, Sung JJY, Chung S. Endoscopic sphincterotomy-induced hemorrhage: A study of risk factors and the role of epinephrine injection. *Gastrointest. Endosc.* 1995; **42**: 550–4.
9 Freeman ML, Nelson DB, Sherman S *et al*. Complications of endoscopic biliary sphincterotomy. *N. Engl. J. Med.* 1996; **335**: 909–19.
10 Nelson DB, Freeman ML. Major hemorrhage from endoscopic sphincterotomy: Risk factor analysis. *J. Clin. Gastroenterol.* 1994; **19**: 283–7.
11 Masci E, Toti G, Mariani A *et al*. Complications of diagnostic and therapeutic ERCP: A prospective multicenter study. *Am. J. Gastroenterol.* 2001; **96**: 417–23.
12 Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. *Gastrointest. Endosc.* 2009; **70**: 80–8.
13 Freeman ML. Understanding risk factors and avoiding complications with endoscopic retrograde cholangiopancreatography. *Curr. Gastroenterol. Rep.* 2003; **5**: 145–53.
14 Hui CK, Lai KC, Yuen MF, Wong WM, Lam SK, Lai CL. Does withholding aspirin for one week reduce the risk of post-sphincterotomy bleeding? *Aliment. Pharmacol. Ther.* 2002; **16**: 929–36.
15 Boustière C, Veitch A, Vanbiervliet G *et al*. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Endoscopy* 2011; **43**: 445–58.
16 Kim KO, Kim TN, Kim SB, Lee JY. Characteristics of delayed hemorrhage after endoscopic sphincterotomy. *J. Gastroenterol. Hepatol.* 2010; **25**: 532–8.
17 Cotton P, Lehman G, Vennes J *et al*. Endoscopic sphincterotomy complications and their management: An attempt at consensus. *Gastrointest. Endosc.* 1991; **37**: 383–93.
18 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.
19 Freeman ML, DiSario JA, Nelson DB *et al*. Risk factors for post-ERCP pancreatitis: A prospective, multicenter study. *Gastrointest. Endosc.* 2001; **54**: 425–34.
20 Anderson MA, Ben-Menachem T, Gan SI *et al*. Management of antithrombotic agents for endoscopic procedures. *Gastrointest. Endosc.* 2009; **70**: 1060–70.
21 Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J. Clin. Pharmacol.* 1995; **35**: 209–19.
22 Komatsu T, Tamai Y, Takami H, Yamagata K, Fukuda S, Munakata A. Study for determination of the optimal cessation period of therapy with anti-platelet agents prior to invasive endoscopic procedures. *J. Gastroenterol.* 2005; **40**: 698–707.
23 Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation* 2007; **115**: 2196–207.