Hemodialysis is a strong risk factor for post-endoscopic sphincterotomy bleeding in patients with choledocholithiasis

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ABSTRACT

Background and study aims Hemodialysis (HD) is considered one of the risk factors for post-endoscopic sphincterotomy (ES) bleeding. Therefore, we conducted a retrospective study to evaluate HD as a risk factor for post-ES bleeding in patients with choledocholithiasis.

Patients and methods We used the post-ES bleeding rate as the main outcome measure. To evaluate the influence of HD on the risk of post-ES bleeding, logistic regression and propensity score analyses were conducted. In addition, univariate analysis-based comparisons of various clinical parameters (as secondary outcome measures) were performed between the patients in the HD and non-HD groups that experienced post-ES bleeding.

Results A total of 1518 patients were enrolled. In the multivariate analysis, a platelet count of <50,000, anticoagulant therapy, bleeding during ES, and HD were found to be significantly associated with post-ES bleeding (odds ratio [OR]: 35.30, 95% confidence interval [CI]: 3.81 – 328.00; OR: 4.39, 95% CI: 1.53 – 12.60; OR: 4.28, 95% CI: 2.30 – 7.97; and OR: 13.30, 95% CI: 5.78 – 30.80, respectively). Propensity score matching created 28 matched pairs. Propensity score analysis showed that the risk difference between the groups was 0.214 (95% CI: 0.022 – 0.407). In a comparison between the patients in the HD and non-HD groups that suffered post-ES bleeding, it was found that the post-ES bleeding was significantly more severe in the HD group (p = 0.033), and massive blood transfusions and long periods of hospitalization were more frequently required in the HD group (p = 0.008 and p < 0.001, respectively).

Conclusion HD is an independent risk factor for post-ES bleeding and makes post-ES bleeding more serious.

Introduction

The first reports about endoscopic sphincterotomy (ES) were produced by Kawai et al. [1] and Classen et al. [2] in the early 1970s. ES has since spread around the world and become the first-choice treatment for choledocholithiasis. Regarding the adverse events associated with ES, post-ES bleeding is often considered to be the most important. It was reported that post-ES bleeding occurs in approximately 1 – 2% of patients who undergo ES. In a systematic review of 21 prospective studies involving 16,855 patients, Andriulli et al. [3] found that post-ES bleeding-related deaths occurred in 0.05% of cases. Many risk factors for post-ES bleeding have been reported, and hemodialysis (HD) is regarded as one of these risk factors [4 – 7]. However, the previous studies that examined this issue were only small observational studies, and they did not control for some important risk factors for post-ES bleeding. Thus, we conducted a retrospective study involving more people to evaluate the influence of HD as the risk factor for post-ES bleeding in patients with choledocholithiasis.

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Patients and methods

This retrospective study was approved by the research ethics committee of Kameda Medical Center.

Patients and data collection

We retrospectively reviewed the medical records of patients who underwent ES at Kameda Medical Center between January 2006 and November 2016. The patient selection criteria were as follows: the patients were required to have naïve papillae and to undergo treatment for choledocholithiasis. The exclusion criteria included malignant biliary obstruction, hemobilia, and not undergoing laboratory tests on the day of ES. Data were collected on the following patient characteristics: age; gender; the platelet count, and international normalized ratio of prothrombin time (PT-INR) on the day of ES; the presence or absence of HD, Child-Pugh class C cirrhosis, a diverticulum, and/ or a surgically altered upper gastrointestinal anatomy (except for a Billroth I anastomosis); and antithrombotic therapy (antiplatelet or anticoagulant therapy). Regarding antithrombotic therapy, the patients were divided into 2 categories (low risk: no medication or adequate drug withdrawal, and high risk: inadequate drug withdrawal or heparinization). The required drug withdrawal periods were defined in accordance with the Japanese guidelines [8]. Concerning the ES procedure, the following data were collected: endoscopists' proficiencies (trainee: ERCP < 200 or ES < 40, expert: ERCP ≥ 200 and ES ≥ 40) [9]; whether endoscopic papillary large balloon dilation (EPLBD) and precut sphincterotomy were performed; and the presence or absence of bleeding during ES. We employed the post-ES bleeding rate as the main outcome measure. Post-ES bleeding was defined as clinically evident bleeding, as set out in the consensus criteria proposed by Cotton et al. [10]. Among the patients that suffered post-ES bleeding, the following clinical parameters were also examined as secondary outcome measures: the pre-ES hemoglobin level, the severity of the post-ES bleeding, the duration of the hospitalization period, the interval between the ES and bleeding, the total number of hemostasis procedures, and the total blood transfusion requirement. The severity of post-ES bleeding was classified as follows: mild bleeding was defined as overt bleeding combined with a reduction in the patient's hemoglobin level to < 3 g/dL, without the need for transfusions; moderate bleeding was defined as a blood transfusion requirement of ≤ 4 units in patients who did not require angiographic interventions or surgery; and severe bleeding was defined as a blood transfusion requirement of ≥ 5 units or the need for angiographic or surgical interventions [10].

ES procedure

The ES procedure was basically carried out with a sphincterotome through a side-viewing duodenoscope (JF-240, TJF-240, JF-260V, TJF-260V; Olympus Medical Systems Co. Ltd., Tokyo, Japan). However, for the patients with surgically altered upper gastrointestinal anatomies (a Billroth II or Roux-en-Y anastomosis), a forward-viewing conventional endoscope (GIF-Q260, PCF-Q240/260, PCF-PQ260L; Olympus Medical Systems) or double balloon endoscope (EN-450T5/W, EC-450BI5; Fujifilm Medical Co. Ltd., Tokyo, Japan) or oblique-viewing endoscope (GIF-XK240; Olympus Medical Systems) was used. The incision length was basically based on the stone size within the oral protrusion (medium ES). However, in the cases of the dilated common bile duct (≥ 12 mm) with the large stone, EPLBD was performed following ES. During the ES, an electrosurgical generator unit (ERBE ICC200; Surgical Technology Group, Hampshire, England, UK) was put in ENDO CUT mode and switched to the 120-W power setting.

Statistical analysis

To evaluate the primary outcome measure, 2 statistical methods were used. First, we performed logistic regression analysis, in which we controlled for variables that exhibited statistically significant associations with post-ES bleeding in the univariate analyses. Second, we carried out propensity score analysis [11]. To calculate the propensity scores, we fitted a covariate balancing propensity score model that predicted HD to the collected variables (age; gender; the presence absence of a platelet count of < 100,000, a PT-INR of > 1.2, HD, Child-Pugh class C cirrhosis, a diverticulum, or a surgically altered upper gastrointestinal anatomy; antiplatelet therapy; and anticoagulant therapy) [12]. One-to-one nearest neighbor matching without replacement was conducted using the log-transformed propensity score. We set the caliper width at 0.001 of the standard deviation of the log-transformed propensity score. We assessed the matched balance between the 2 groups based on the standardized mean difference, and an absolute standardized mean difference of < 0.1 was considered to indicate that the relevant covariate was balanced. To evaluate the post-ES bleeding risk for matched groups, the risk difference (RD) was calculated. Next, to evaluate the secondary outcome measures, univariate analyses of these clinical parameters were performed via comparisons between the patients in the HD and non-HD groups that suffered post-ES bleeding. In the univariate analyses, categorical variables were analyzed using the χ^2-test or Fisher's exact test, whereas continuous variables were analyzed using the t-test. A p-value of < 0.05 was regarded as statistically significant. We used R 3.3.0 to perform the statistical analyses. The Matchit package and CBPS package were also used for the propensity score analysis [13, 14].

Results

A total of 6883 endoscopic retrograde cholangiopancreatography procedures, including 2361 ES procedures, were performed during the study period. Of the patients that underwent these procedures, 1518 met the abovementioned criteria (HD group: n = 38, non-HD group: n = 1480). The patients' baseline characteristics are summarized in ▶ Table 1. A total of 50 patients experienced post-ES bleeding (3.3 %). The risk of post-ES bleeding was 29.0 % (11/38) in the HD group, whereas it was 2.6 % (39/1480) in the non-HD group.

The results of the univariate and multivariate analyses are shown in ▶ Table 2. The platelet count, a platelet count of < 100,000, a platelet count of < 50,000, antithrombotic therapy,

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▶ **Table 1** Patients' baseline characteristics.

Factor	Group	n/mean ± SD	%
Total		1518	
Age		74.70 ± 12.84	
Gender	F	705	46.4
	M	813	53.6
Diverticulum	–	996	65.6
	+	522	34.4
Surgically altered upper gastrointestinal anatomy	–	1446	95.3
	+	72	4.7
LC (Child-Pugh class C)	–	1506	99.2
	+	12	0.8
HD	–	1480	97.5
	+	38	2.5
Antiplatelet therapy	none	1284	84.6
	adequate drug withdrawal	209	13.8
	inadequate drug withdrawal	25	1.6
Anticoagulant therapy	none	1439	94.8
	adequate drug withdrawal	29	1.9
	heparinization	47	3.1
	inadequate drug withdrawal	3	0.2
Platelet count		20.68 ± 8.17	
▪ <100,000		88	5.8
▪ <50,000		4	0.3
PT-INR		1.06 ± 0.13	
▪ >1.2		161	10.6
▪ >1.5		12	0.8
Precut sphincterotomy	–	1426	93.9
	+	92	6.1
EPLBD	–	1500	98.8
	+	18	1.2

LC: liver cirrhosis; SD: standard deviation

anticoagulant therapy, bleeding during ES, and HD were found to be significantly associated with post-ES bleeding in the univariate analyses ($P = 0.008$, $P = 0.022$, $P = 0.006$, $P = 0.033$, $P = 0.022$, $P < 0.001$, and $P < 0.001$, respectively). In the multivariate analysis controlling for a platelet count of < 50,000, anticoagulant therapy, bleeding during ES, and HD, all of these variables

exhibited significant associations with post-ES bleeding (odds ratio [OR]: 35.30, 95 % confidence interval [CI]: 3.81 – 328.00, p = 0.002; OR: 4.39, 95 % CI: 1.53 – 12.60, $P = 0.006$; OR: 4.28, 95 % CI: 2.30 – 7.97, $P < 0.001$; and OR: 13.30, 95 % CI: 5.78 – 30.80, $P < 0.001$, respectively).

Using propensity score matching, 28 matched pairs were created. The baseline characteristics of all patients and the matched patients are summarized in ▶ **Table 3**. The propensity score analysis showed that the mean RD was 0.214 (95 % CI: 0.022 – 0.407) (▶ **Table 4**).

In a comparison of the patients in the HD group that suffered post-ES bleeding with those in the non-HD group (▶ **Table 5**), it was found that post-ES bleeding was significantly more severe in the HD group ($P = 0.033$), and massive blood transfusions and long periods of hospitalization were more frequently required in the HD group ($P = 0.008$ and $P < 0.001$, respectively). A post-ES bleeding-related death occurred in the non-HD group.

Discussion

The present study revealed that post-ES bleeding occurred in 29.0 % of HD patients, which agrees with the findings of previous reports (15.8 – 50 %) [4 – 7]. Therefore, it was confirmed that HD is an important risk factor for post-ES bleeding. On the other hand, the result of the propensity score analysis – i. e., that the RD was 0.214 (95 % CI: 0.022 – 0.407) – was considered a novel finding.

Regarding other risk factors, antithrombotic therapy was reported to be an important risk factor for post-ES bleeding [15]. In addition, the number of reports that have concluded that heparinization caused bleeding events easily has been increasing [7, 16]. This study also showed the same result. In general, HD patients are at higher risk of cardiovascular events than non-HD patients [17]; hence, it is considered that the frequency of antithrombotic therapy is also higher among HD patients. Although the current study did not detect a significant difference in the frequency of antithrombotic therapy between the HD and non-HD groups, post-ES bleeding occurred more frequently in the HD group. These results suggest that HD is an independent risk factor for antithrombotic therapy. On the other hand, a low platelet count was also recognized as a risk factor for post-ES bleeding. In the current study, a platelet count of < 50,000 was found to be strongly correlated with post-ES bleeding in the univariate analyses. However, it was considered that HD and a low platelet count were confounding variables because the mean platelet count of the HD group was significantly lower than that of the non-HD group. To confirm that HD is an independent risk factor for post-ES bleeding, we needed to eliminate the influences of other risk factors. Therefore, we conducted a propensity score analysis in addition to a logistic regression analysis. As far as we know, this is the first English language study to have evaluated the influence of HD as a risk factor for post-ES bleeding using propensity score analysis. The propensity score analysis also showed that the risk of post-ES bleeding was higher in the HD group than in the non-HD group; however, the difference was not statistically significant. It was

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▶ **Table 2** The results of the univariate and multivariate analyses of the characteristics of the patients who did and did not suffer post-ES bleeding.

Factor	Group	Post-ES bleeding		Univariate analysis	Multivariate analysis	
		–	+	*P*-value	*P*-value	OR (95 % CI)
n		1468	50			
Age (mean ± SD)		74.78 ± 12.84	72.44 ± 12.83	0.206		
Gender (%)	F	685 (46.7)	20 (40.0)	0.389		
	M	783 (53.3)	30 (60.0)			
Diverticulum (%)	–	961 (65.5)	35 (70.0)	0.548		
	+	507 (34.5)	15 (30.0)			
Surgically altered upper gastrointestinal anatomy (%)	–	1397 (95.2)	49 (98.0)	0.729		
	+	71 (4.8)	1 (2.0)			
LC (Child-Pugh class C) (%)	–	1456 (99.2)	50 (100.0)	1		
	+	12 (0.8)	0 (0.0)			
HD (%)	–	1441 (98.2)	39 (78.0)	<0.001	<0.001	13.30 (5.78 – 30.80)
	+	27 (1.8)	11 (22.0)			
Antithrombotic therapy (%)	none/adequate drug withdrawal	1399 (95.3)	44 (88.0)	0.033		
	heparinization/inadequate drug withdrawal	69 (4.7)	6 (12.0)			
Antiplatelet therapy (%)	none/adequate drug withdrawal	1444 (98.4)	49 (98.0)	0.57		
	inadequate drug withdrawal	24 (1.6)	1 (2.0)			
Anticoagulant therapy (%)	none/adequate drug withdrawal	1423 (96.9)	45 (90.0)	0.022	0.006	4.39 (1.53 – 12.60)
	heparinization/inadequate drug withdrawal	45 (3.1)	5 (10.0)			
Platelet count (mean ± SD)		20.79 ± 8.19	17.66 ± 7.13	0.008		
▪ <100,000	–	1387 (94.5)	43 (86.0)	0.022		
	+	81 (5.5)	7 (14.0)			
▪ <50,000	–	1466 (99.9)	48 (96.0)	0.006	0.002	35.30 (3.81 – 328.00)
	+	2 (0.1)	2 (4.0)			
PT-INR (mean ± SD)		1.06 ± 0.13	1.05 ± 0.11	0.647		
▪ >1.2	–	1313 (89.4)	44 (88.0)	0.645		
	+	155 (10.6)	6 (12.0)			
▪ >1.5	–	1456 (99.2)	50 (100.0)	1		
	+	12 (0.8)	0 (0.0)			
Endoscopists' proficiencies (%)	expert	552 (37.6)	17 (34.0)	0.658		
	trainee	916 (62.4)	33 (66.0)			
Precut sphincterotomy (%)	–	1379 (93.9)	47 (94.0)	1		
	+	89 (6.1)	3 (6.0)			

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▶ **Table 2** (Continuation)

Factor	Group	Post-ES bleeding −	Post-ES bleeding +	Univariate analysis P-value	Multivariate analysis P-value	OR (95 % CI)
EPLBD (%)	−	1452 (98.9)	48 (96.0)	0.116		
	+	16 (1.1)	2 (4.0)			
Bleeding during ES (%)	−	1269 (86.4)	30 (60.0)	<0.001	<0.001	4.28 (2.30 – 7.97)
	+	199 (13.6)	20 (40.0)			

LC: liver cirrhosis, SD: standard deviation

▶ **Table 3** The baseline characteristics of the unmatched and propensity-matched groups of patients.

Factor	Group	HD −	HD +	Unmatched group SMD	HD −	HD +	Matched group SMD
n		1480	38		28	28	
Age (mean ± SD)		74.80 ± 12.90	70.68 ± 9.27	0.366	71.64 ± 9.84	71.18 ± 9.42	0.048
Gender (%)	F	689 (46.6)	16 (42.1)	0.090	14 (50.0)	15 (53.6)	0.072
	M	791 (53.4)	22 (57.9)		14 (50.0)	13 (46.4)	
Diverticulum (%)	−	971 (65.6)	25 (65.8)	0.004	16 (48.1)	17 (65.4)	0.223
	+	509 (34.4)	13 (34.2)		12 (42.9)	9 (34.6)	
Surgically altered upper gastrointestinal anatomy (%)	−	1411 (95.3)	35 (92.1)	0.132	28 (100.0)	27 (96.4)	0.272
	+	69 (4.7)	3 (7.9)		0 (0.0)	1 (3.6)	
LC (Child-Pugh class C) (%)	−	1468 (99.2)	38 (100.0)	0.128	28 (100.0)	28 (100.0)	NaN
	+	12 (0.8)	0 (0.0)		0 (0.0)	0 (0.0)	
Platelet count	≥100,000	1400 (94.6)	30 (78.9)	0.470	28 (100.0)	28 (100.0)	NaN
	<100,000	80 (5.4)	8 (21.1)		0 (0.0)	0 (0.0)	
PT-INR	≤1.2	1320 (89.2)	37 (97.4)	0.330	28 (100.0)	27 (96.4)	0.272
	>1.2	160 (10.8)	1 (2.6)		0 (0.0)	1 (3.6)	
Antiplatelet therapy (%)	none/adequate drug withdrawal	1455 (98.3)	38 (100.0)	0.185	28 (100.0)	28 (100.0)	NaN
	inadequate drug withdrawal	25 (1.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Anticoagulant therapy (%)	none/adequate drug withdrawal	1431 (96.7)	37 (97.4)	0.040	28 (100.0)	27 (96.4)	0.272
	heparinization/inadequate drug withdrawal	49 (3.3)	1 (2.6)		0 (0.0)	1 (3.6)	

SMD: standardized mean difference, LC: liver cirrhosis, SD: standard deviation, NaN: not a number

considered that the lack of significance resulted from a deficiency of matched pairs.

It is deemed that HD is a risk factor for post-ES bleeding; however, there have only been a few reports about the relationship between post-ES bleeding and HD [4 – 7]. Moreover, the

previous studies about this topic had some limitations. For example, they only included 14, 6, 21, and 19 HD patients who underwent ES, respectively. Based on multiple logistic regression analysis involving 6 variables, Nelson et al. [4] concluded that HD was the strongest risk factor for post-ES bleeding; how-

▶ **Table 4** The results of the propensity score analysis.

	Unmatched group		RD (95 % CI)	Matched group		RD (95 % CI)
HD	–	+		–	+	
n	1480	38		28	28	
Post-ES bleeding (%)	39 (2.6)	11 (28.9)	0.263 (0.119 – 0.408)	3 (10.7)	8 (28.6)	0.214 (0.022 – 0.407)

▶ **Table 5** The results of univariate analyses of the clinical parameters of the patients who experienced post-ES bleeding.

		HD		Univariate analysis
Factor	Grade	–	+	P-value
n		39	11	
Severity (%)	mild	24 (61.5)	3 (27.3)	0.033
	moderate	12 (30.8)	4 (36.4)	
	severe	3 (7.7)	4 (36.4)	
Interval between ES and bleeding (days) (median [range])		3 [0 – 10]	4 [1 – 7]	0.392
Median duration of hospitalization (days) (median [range])		9 [1 – 261]	15 [3 – 164]	<0.001
Median blood transfusion requirement (IU) (median [range])		0 [0 – 20]	4 [0 – 26]	0.008
Median number of hemostasis procedures (median [range])		1 [0 – 4]	2 [0 – 8]	0.085
Median pre-ES Hb level (mg/dL) (median [range])		13.0 [8.0 – 17.1]	9.8 [8.8 – 12.3]	0.001
Hb: hemoglobin				

ever, there were only 10 patients who suffered post-ES bleeding in their study. Therefore, the number of variables selected for the logistic regression analysis was excessive. Such models are called "overfitted" models and can result in spurious findings of significance and unreliable estimates of the magnitudes of detected associations [18]. In terms of the number of HD patients who underwent ES, the study by Hori et al. [6] was superior to the other studies; however, it was an uncontrolled study. The present study included 50 patients who suffered post-ES bleeding, which was sufficient to allow us to perform a logistic regression analysis involving 3 variables.

Furthermore, in this study we clarified that post-ES bleeding was more severe and a longer period of hospitalization was required in the HD group compared with the non-HD group. The severity of post-ES bleeding was assessed based on the total blood transfusion requirement; hence, it was presumed that massive bleeding occurred in the HD group. In general, it has been reported that uremia-induced platelet dysfunction (due to reductions in the aggregation abilities and adhesiveness of platelets) and intermittent anticoagulant use during HD increase the risk of bleeding in HD patients [19]. It is likely that these factors affect not only whether bleeding occurs, but also how long it continues for. Moreover, delayed wound healing caused by malnutrition, peripheral circulatory failure, and immunodeficiency can prolong bleeding [20].

However, our study also has some limitations. First, many candidates were excluded from this study because of data deficiencies (although it still involved more HD patients than pre-vious studies that examined this issue). Therefore, this study might have been affected by sampling bias. Second, propensity score matching indicated that the 2 groups were not completely balanced. Hence, the results of the propensity score analysis are not definitive. Third, the patients' hemoglobin levels were not regulated. Among the patients who suffered post-ES bleeding, the median pre-ES hemoglobin level was significantly lower in the HD group. Therefore, regardless of the volume of intraoperative hemorrhaging, the HD group might have had a much greater blood transfusion requirement, which was used to assess the severity of post-ES bleeding, than the non-HD group.

In conclusion, logistic regression analysis indicated that HD is an independent risk factor for post-ES bleeding and makes post-ES bleeding more severe. In the future, we should perform a further study involving a greater number of HD patients to identify additional risk factors for post-ES bleeding.

Competing interests

None

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