

[ORIGINAL ARTICLE]

The Incidence of Complications in Single-stage Endoscopic Stone Removal for Patients with Common Bile Duct Stones: A Propensity Score Analysis

Hirokazu Saito^{1,2}, Yoshihiro Kadono³, Kentaro Kamikawa³, Atsushi Urata³, Haruo Imamura³,
Ikuo Matsushita², Tatsuyuki Kakuma⁴ and Shuji Tada¹

Abstract:

Objective Single-stage endoscopic stone removal for choledocholithiasis is an advantageous approach because it is associated with a shorter hospital stay; however, few studies have reported the incidence of complications related to this procedure in detail. The aim of this study was to examine the incidence of complications and efficacy of this procedure.

Methods This retrospective study investigated the incidence of complications in 345 patients with naive papilla who underwent therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis at three institutions between April 2014 and March 2016 by a propensity score analysis. The efficacy of single-stage endoscopic stone removal was assessed based on a hospital stay of within 7 days and the number of ERCP attempts.

Results Among 114 patients who underwent single-stage endoscopic stone removal, 15 patients (13.2%) experienced complications. Among the remaining 231 patients in the two-stage endoscopic stone removal group, complications were observed in 17 patients (7.4%). The propensity score analysis, which was adjusted for confounding factors, revealed that single-stage endoscopic stone removal was not a significant risk factor for complications ($p=0.52$). In patients in whom >10 min was required for deep cannulation, single-stage endoscopic stone removal was not a significant risk factor for complications in the propensity score analysis ($p=0.37$). In the single-stage group, the proportion of patients with a hospital stay of within 7 days was significantly higher and the number of ERCP attempts was significantly lower in comparison to the two-stage group ($p<0.0001$ and <0.0001 , respectively).

Conclusion Single-stage endoscopic stone removal did not increase the incidence of complications associated with ERCP and was effective for reducing the hospital stay and the number of ERCP attempts.

Key words: single-stage endoscopic stone removal, common bile duct stones, complications, propensity score analysis

(Intern Med 57: 469-477, 2018)

(DOI: 10.2169/internalmedicine.9123-17)

Introduction

Endoscopic stone removal is the first choice of treatment for choledocholithiasis (1); however, the performance of endoscopic retrograde cholangiopancreatography (ERCP) dur-

ing stone removal is associated with a high risk of complications such as pancreatitis, cholangitis, bleeding, and perforation (2). Endoscopic stone removal requires endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilation (EPBD). In approximately 90% of the cases, endoscopic stone removal is possible following EST and EPBD

¹Department of Gastroenterology, Kumamoto City Hospital, Japan, ²Department of Gastroenterology, Kumamoto Chuo Hospital, Japan, ³Department of Gastroenterology, Saiseikai Kumamoto Hospital, Japan and ⁴Department of Biostatistics Center, Medical School, Kurume University, Japan

Received: March 1, 2017; Accepted: July 5, 2017; Advance Publication by J-STAGE: November 20, 2017

Correspondence to Dr. Hirokazu Saito, arnestwest@yahoo.co.jp

using a basket or balloon (3, 4). For large common bile duct stones (CBDSs), endoscopic stone removal is achieved with a mechanical lithotripter (5, 6) or endoscopic large balloon dilation (EPLBD) (7). Thus, endoscopic stone removal is increasingly used based on the high success rate. However, because the calculus must be passed through the papilla, the potential for major damage to the papilla and the increased risk of complications are cause for concern.

In addition to EST and EPBD, the safe implementation of single-stage endoscopic stone removal is potentially advantageous as it has the potential to reduce the hospital stay and the associated medical costs. With the exception of cases involving moderate to severe cholangitis (8), single-stage endoscopic stone removal is generally recommended for choledocholithiasis; however, few studies have reported the incidence of complications of single-stage endoscopic stone removal in detail, and the decision to perform single-stage endoscopic stone removal remains at the discretion of the individual endoscopist.

The aim of the present study was to compare the incidence of complications in patients with naive papilla undergoing the removal of CBDSs via EST, EPBD or EPLBD by single-stage endoscopy to the incidence in patients undergoing two-stage endoscopic stone removal, with the aim of assessing the efficacy of single-stage endoscopic stone removal.

Materials and Methods

Study design

In this retrospective observational study, the medical records database of the patients with CBDSs who were treated with ERCP between April 2014 and March 2016 at three tertiary care centers, Kumamoto City Hospital, Saiseikai Kumamoto Hospital, and Kumamoto Chuo Hospital, was reviewed. This study was approved by the institutional review board of each participating institution.

The study population included patients with naive papilla who were treated with ERCP using EST, EPBD or EPLBD. None of the patients had a history of abdominal surgery or had undergone Billroth I gastrectomy in the past. The exclusion criteria were as follows: [1] unsuccessful deep cannulation in the first session, [2] moderate or severe cholangitis because CBDS removal was recommended after biliary drainage and for the improvement of the general condition of these patients (8), [3] biliary pancreatitis meeting the criteria of moderate or severe cholangitis, and [4] prior Billroth II anastomosis or Roux-en-Y gastric reconstruction. After applying the exclusion criteria, 345 patients were included in the final analysis.

The endoscopists and the devices used for stone removal

All ERCP procedures were conducted by 20 different endoscopists, these included trainees (n=8), as well as

intermediate-level (n=6) and expert (n=6) endoscopists. Expert endoscopists with advanced skills were those who were capable of single-handedly completing procedures that corresponded to grade 3 in the ERCP grading scale that was reported in the core curriculum published in 2016 (9); intermediate-level endoscopists were capable of single-handedly completing procedures that corresponded to grade 2. Trainee endoscopists were those capable of completing procedures that corresponded to grade 1 or those who had performed ERCP in <200 cases.

Side-viewing duodenoscopy (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan) was performed in all cases, and the CBDSs were removed via a basket and/or balloon catheter and/or mechanical lithotripter.

Study definitions

The single-stage endoscopic stone removal and two-stage endoscopic stone removal groups

Single-stage endoscopic stone removal was defined as CBDS removal in addition to EST or EPBD.

Two-stage stone removal was defined as CBDS removal in two stages. In the first stage, biliary drainage in addition to EST or EPBD was performed. In the second stage (a few days after the first stage), the CBDSs were removed.

Asymptomatic and symptomatic CBDSs

Asymptomatic CBDSs were defined by the absence of symptoms and CBDS-associated blood test abnormalities at the time of ERCP. Symptomatic CBDSs included cholangitis, jaundice, biliary pancreatitis, calculus impaction, and elevated liver enzyme levels.

Complications

Complications associated with ERCP were defined as any complication occurring after the ERCP procedure that required more than one day of hospitalization. If a patient had several complications, the most severe complication was selected. In the present study, post-ERCP pancreatitis (PEP) and bleeding and perforation were defined and graded based on the consensus criteria established by Cotton et al. (10). Cholangitis was diagnosed and graded based on the 2013 Tokyo Guidelines (8).

Post-ERCP pancreatitis

The criteria for the diagnosis of PEP included new or worsening abdominal pain requiring hospitalization for one or more nights beyond the planned admission, accompanied by a serum amylase concentration 3 times above the upper limit of normal at 24 h after ERCP. Mild and moderate PEP were defined as hospitalization for 2-3 and 4-10 days, respectively, whereas severe PEP was defined as PEP requiring hospitalization for >10 days requiring percutaneous drainage or surgery.

Bleeding

Bleeding was defined as procedure-related bleeding with

melena, hematemesis, or a decrease in the hemoglobin concentration. Bleeding was graded as mild if the decrease in hemoglobin was <30 g/L and no blood transfusion was required, moderate if up to 4 units of red blood cells were transfused, and severe if blood transfusion of ≥ 5 units, surgery, or angiography was required.

Perforation

The diagnosis of perforation was based on the presence of air or contrast medium in the retroperitoneal space on abdominal CT. Perforation was only graded as mild if the leak of fluid or contrast medium was very slight and resolved within ≤ 3 days, whereas moderate perforation required medical treatment for 4-10 days. Perforation was graded as severe if medical treatment for >10 days, percutaneous drainage, or surgery was necessary.

Cholangitis

For the definitive diagnosis of cholangitis, the presence of at least one criterion from the systemic inflammation category, one criterion from the cholestasis category, and one criterion from the imaging category was required.

1) Systematic inflammation:

- Fever $>38^{\circ}\text{C}$ and/or shaking chills
- Evidence of an inflammatory response based on the following laboratory data: white blood cell (WBC) count, $<4.0 \times 10^9/\text{L}$ or $>10 \times 10^9/\text{L}$ and C-reactive protein (CRP), ≥ 9.52 nmol/L

2) Cholestasis:

- Jaundice: total bilirubin ≥ 34.2 $\mu\text{mol/L}$
- Abnormal liver function tests: alanine aminotransferase $>1.5 \times$ upper limit of normal value (ULN), aspartate aminotransferase $>1.5 \times$ ULN, γ -glutamyl transferase $>1.5 \times$ ULN, and alkaline phosphatase $>1.5 \times$ ULN

3) Imaging:

- Biliary dilatation
- Evidence of etiology on imaging

Severe acute cholangitis was diagnosed in cases that fulfilled at least one of the following criteria: hypotension requiring dopamine ≥ 5 $\mu\text{g/kg/min}$ or any dose of norepinephrine, altered consciousness, partial pressure of arterial oxygen (PaO_2)/ FiO_2 ratio <300 , oliguria or serum creatinine >176.8 $\mu\text{mol/L}$, prothrombin time/international normalized ratio >1.5 , platelet count $<100 \times 10^9/\text{L}$. Moderate acute cholangitis was diagnosed in cases that met any two of the following conditions: WBC count $>12 \times 10^9/\text{L}$ or $<4 \times 10^9/\text{L}$, fever $\geq 39^{\circ}\text{C}$, age ≥ 75 years, hyperbilirubinemia (total bilirubin ≥ 85.5 $\mu\text{mol/L}$), hypoalbuminemia ($<\text{standard} \times 7$ g/L). Cases that did not meet the criteria of severe or moderate acute cholangitis were diagnosed with mild cholangitis.

Statistical analysis

The association between complications and single-stage endoscopic stone removal were investigated in two stages. We first evaluated the association between the complication status and each risk factor separately, and then factors with

p values <0.2 were entered into a multivariate logistic regression model. In the second stage, we examined the association between the single-stage endoscopic stone removal status and risk factors that were identified in the first stage. Risk factors with p values of <0.10 that were found to be associated with both complications and single-stage endoscopic stone removal in the univariate analysis were identified as potential confounders (shown as propensity score group 1). In addition, risk factors that were known as procedure-related risk factors and patient-related risk factors were listed as other potential confounders (shown as propensity score group 2 and propensity score group 3, respectively). Before examining the effect of single-stage endoscopic stone removal on the occurrence of complications, these three groups of confounding factors were converted to propensity scores based on a logistic regression analysis, and adjusted odds ratios (ORs) between single-stage endoscopic stone removal and complications were calculated.

The chi-squared test or Fisher's exact test were performed in the univariate analyses, and p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP[®] Pro software program (version 12, SAS Institute, Cary, USA).

Results

The rate of successful deep cannulation in the first session

Among a total of 356 patients who met inclusion criteria of this study, deep cannulation was successfully performed in the first session in 345 (96.9%) patients; deep cannulation in the first session failed in the remaining 11 (3.1%) patients who were therefore excluded from the subsequent analysis. Thus, 345 patients were included in the final analysis.

Indications for ERCP

The indications for ERCP included asymptomatic CBDSs ($n=64$; 18.6%) and symptomatic CBDSs ($n=281$; 81.4%) patients. The causes of symptomatic CBDSs included mild cholangitis ($n=130$; 37.7%), biliary pancreatitis ($n=39$; 11.3%), calculus impaction ($n=15$; 4.3%), jaundice ($n=46$; 13.3%), and elevated liver enzyme levels ($n=49$; 14.2%).

The incidence of ERCP-related complications

Among the 345 patients, 114 (33.0%) patients underwent single-stage endoscopic stone removal. A total of 32 (9.3%) patients in the entire analysis cohort ($n=345$) experienced complications including pancreatitis ($n=16$; 4.6%), cholangitis ($n=6$; 1.7%), perforation ($n=4$; 1.2%), and hemorrhage ($n=6$; 1.7%). The complications were mild in 13 cases (40.6%) and moderate or severe in 19 cases (59.4%).

Table 1. The Demographics and Characteristics of the Patients in Single-stage Endoscopic Stone Removal and Two-stage Endoscopic Stone Removal Groups.

	Single-stage endoscopic stone removal	Two-stage endoscopic stone removal	p value
Significant in the univariate analysis			
Biliary stent placement (Yes/no)	63 (18.3%)/51 (14.8%)	225 (65.2%)/6 (1.7%)	<0.0001
Indication for ERCP (Asymptomatic/symptomatic)	35(10.1%)/79 (22.9%)	29 (8.4%)/202 (58.6%)	0.0001
Serum bilirubin (Normal/elevated)	64 (18.6%)/50 (14.5%)	81 (23.5%)/150 (43.5%)	0.0003
Pancreatic stent placement (Yes/no)	3 (0.87%)/111 (32.8%)	45 (13.0%)/186 (53.9%)	<0.0001
Time of deep cannulation (≤ 10 min/ > 10 min)	87(25.2%)/27(7.8%)	149(43.2%)/82(23.8%)	0.027
Endoscopist's experience (Expert/intermediate/trainee)	42(12.2%)/38(11.0%)/34 (9.9%)	126 (36.5%)/55(15.9%)/50 (14.5%)	0.0083
Antibiotics (Yes/no)	64 (18.6%)/50 (14.5%)	174 (50.4%)/57 (16.5%)	0.0005
Pancreatic injection (Yes/no)	45 (13.0%)/69 (20.0%)	131 (38.0%)/100 (29.0%)	0.0029
Stone size (< 10 mm/ ≥ 10 mm)	97 (28.1%)/17 (4.9%)	169 (49.0%)/62 (18.0%)	0.014
Diameter of common bile duct (< 10 mm/ ≥ 10 mm)	65 (18.8%)/49 (14.2%)	89 (25.8%)/142 (41.2%)	0.0013
Not significant			
Age (< 75 yr/ ≥ 75 yr)	67 (19.4%)/47 (13.6%)	115 (33.3%)/116 (33.6%)	0.14
Gender(M/F)	64 (18.6%)/50 (14.5%)	129 (37.4%)/102 (29.6%)	1.0
History of abdominal surgery (No surgery/Billroth I)	113 (32.8%)/1 (0.29%)	227 (65.8%)/4 (1.2%)	1.0
Coexisting illness (Yes/no)	47 (13.6%)/67 (19.4%)	114 (33.0%)/117 (33.9%)	0.17
Antithrombotic drug (Yes/no)	28 (8.1%)/86 (24.9%)	53 (15.4%)/178 (51.6%)	0.79
Chemoprevention (Yes/no)	40 (11.6%)/74 (21.5%)	72 (20.9%)/159 (46.1%)	0.47
Sphincterotomy technique (EST $\pm$ precut)/EPBD	102 (29.6%)/12 (3.5%)	211 (61.2%)/20 (5.8%)	0.56
Stone number (≤ 1 / ≥ 2)	73 (21.2%)/41 (11.9%)	160 (46.4%)/71 (20.6%)	0.33
Gallstones (Absence/presence)	39 (11.3%)/75(21.7%)	85 (24.6%)/146(42.3%)	0.72
Gallbladder (Post-cholecystectomy/presence)	10 (2.9%)/104(30.1%)	25 (7.3%)/206(59.7%)	0.71

ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilation

The demographics and characteristics of the patients in the single-stage and two-stage endoscopic stone removal groups

The details of the demographics and characteristics of the patients in both groups are shown in Table 1. Few patients underwent precut sphincterotomy and were thus included in the EST group. EPLBD was included as EPBD because only two patients underwent the procedure. Ten factors were found to be significant in the univariate analysis: biliary stent placement, indication for ERCP, serum bilirubin, pancreatic stent placement, time of deep cannulation, the endoscopist's experience, antibiotics, pancreatic injection, stone size, and the diameter of common bile duct.

The risk factors for ERCP-related complications

The results of the univariate and multivariate analyses of the risk factors for ERCP-related complications are shown in

Tables 2 and 3. Among the 114 patients who underwent single-stage endoscopic stone removal, 15 patients (13.2%) experienced complications, which included pancreatitis ($n=10$; 8.8%), cholangitis ($n=3$; 2.6%), bleeding ($n=1$; 0.88%), and perforation ($n=1$; 0.88%). Among the 231 patients who underwent two-stage endoscopic stone removal, 17 patients (7.4%) had complications. Single-stage endoscopic stone removal was not found to be a significant risk factor by either the univariate or multivariate analyses ($p=0.11$ and $p=0.69$, respectively). The results of the propensity score analysis are shown in Table 4. Single-stage endoscopic stone removal was not significantly associated with ERCP-related complications after adjusting for confounding factors (odds for complication = 1.4, $p=0.52$, 95% CI=0.52-3.5).

Risk factors for PEP

In an analysis limited to the incidence of PEP, antibiotics and antithrombotic drug were excluded from the risk factors

Table 2. Univariate Analyses of Risk Factors for ERCP-related Complications.

	With complications	Without complications	p value
Significant by univariate analysis			
Indication of ERCP (Symptomatic/asymptomatic)	14 (4.1%)/18 (5.2%)	267 (77.4%)/46 (13.3%)	<0.0001
Time of deep cannulation (≤10 min/>10 min)	15 (4.4%)/17 (4.9%)	221 (64.1%)/92 (26.7%)	0.0088
Serum bilirubin (Normal/elevated)	21 (6.1%)/11 (3.2%)	124 (35.9%)/189 (54.8%)	0.0076
Biliary stent placement (Yes/no)	20 (5.8%)/12 (3.5%)	268 (77.7%)/45 (13.0%)	0.0022
Antibiotics (Yes/no)	17 (4.9%)/15 (4.4%)	221 (64.1%)/92 (26.7%)	0.047
Not significant			
Single-stage endoscopic stone removal (Yes/no)	15 (4.4%)/17 (4.9%)	99 (28.7%)/214 (62.0%)	0.11
Age (<75 yr/≥75 yr)	13 (3.8%)/19(5.5%)	169 (49.0%)/144(41.7%)	0.19
Gender (M/F)	18 (5.2%)/14(4.1%)	175 (50.7%)/138(40.0%)	1.00
Endoscopist's experience (Expert/intermediate/trainee)	15 (4.6%)/9(2.6%) / 8 (2.3%)	153 (44.4%)/84 (24.4%) / 76 (22.0%)	0.98
History of abdominal surgery (No surgery/Billroth I)	32 (9.3%)/0 (0%)	308 (89.3%)/5 (1.5%)	1.0
Coexisting illness (Yes/No)	16 (4.6%)/16(4.6%)	145 (42.0%)/168 (48.7%)	0.71
Antithrombotic drug (Yes/no)	8 (2.3%)/24 (7.0%)	73 (21.2%)/240 (69.6%)	0.83
Chemoprevention (Yes/no)	6 (1.7%)/26 (7.5%)	106 (30.7%)/207 (60.0%)	0.11
Sphincterotomy technique (EST ± precut/EPBD)	28 (8.1%)/4 (1.2%)	285 (82.6%)/28 (8.1%)	0.52
Pancreatic injection (Yes/no)	19 (5.5%)/13(3.8%)	157 (45.5%)/156 (45.2%)	0.36
Pancreatic stent placement (Yes/no)	7 (2.0%)/25 (7.3%)	41 (11.9%)/272 (78.8%)	0.18
Stone number (≤1/≥2)	26 (7.5%)/6 (1.7%)	207 (60.0%)/106 (30.7%)	0.11
Stone size (<10 mm/≥10 mm)	25 (7.3%)/7 (2.0%)	241 (69.9%)/72 (20.9%)	1.0
Diameter of common bile duct (<10 mm/≥10 mm)	17 (4.9%)/15 (4.4%)	137 (39.7%)/176 (51.0%)	0.35
Gallstones (absence/presence)	12 (3.5%)/20 (5.8%)	112 (32.5%)/201 (58.3%)	0.85
Gallbladder (Post-cholecystectomy/presence)	4 (1.2%)/28 (8.1%)	31 (9.0%)/282 (81.7%)	0.55

ERCP: endoscopic retrograde cholangiopancreatography, EST: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilation

Table 3. Multivariate Analysis of Risk Factors for ERCP-related Complications.

	Odds ratio	95% CI	p value
Single-stage endoscopic stone removal (Yes)	1.2	0.36-4.2	0.69
Indication for ERCP (Asymptomatic CBDs)	6.8	2.4-20.3	0.0003
Time of deep cannulation (>10 min)	2.3	0.99-5.5	0.053
Serum bilirubin (Normal)	0.95	0.34-2.6	0.93
Biliary stent placement (No)	2.3	0.70-8.0	0.17
Antibiotics (No)	0.65	0.22-1.8	0.40
Pancreatic stent placement (Yes)	2.0	0.62-6.2	0.24
Age (≥75 yr)	2.0	0.87-4.8	0.11
Chemoprevention (No)	2.0	0.76-6.3	0.16
Stone number (≤1)	2.4	0.92-7.2	0.075

ERCP: endoscopic retrograde cholangiopancreatography, CBDs: common bile duct stones, CI: confidence interval

because these factors are not risk factors for PEP. Among the 231 patients who underwent two-stage endoscopic stone removal, 6 patients (2.6%) developed PEP. Six risk factors were found to be significant in the univariate analysis: among the 114 patients who underwent single-stage endoscopic stone removal, 10 patients (8.8%) developed PEP. Among

Table 4. Effect of Single-stage Endoscopic Stone Removal on Complications after Controlling for Confounding Factors.

	Odds ratio	p value/(95% CI)
Single-stage endoscopic stone removal	1.4	0.52 / (0.52-3.5)
Propensity score group1 [‡]		0.010
Propensity score group2 [§]		0.16
Propensity score group3 ^{**}		0.69

CI: confidence interval

[‡]Risk factors that were associated with both complications and single-stage endoscopic stone removal in univariate analysis: indication for ERCP, time of deep cannulation, serum bilirubin, biliary stent placement, and antibiotics were included.[§]Procedure-related risk factors associated with complications in previous studies: endoscopist's experience, sphincterotomy technique, pancreatic injection, chemo-prevention, and pancreatic stent placement were included.^{**}Patient-related risk factors associated with complications in previous studies: age, sex, coexisting illness, antithrombotic drug, diameter of common bile duct, stone size, stone number, gallstones, and gallbladder were included.**Table 5. Effect of single-stage endoscopic stone removal on complications after controlling for confounding factors in patients requiring more than 10 minutes for deep cannulation.**

	Odds ratio	p value/(95% CI)
Single-stage endoscopic stone removal	2.2	0.37 / (0.39-12.8)
Propensity score group1 [‡]		0.0011
Propensity score group2 [§]		0.26
Propensity score group3 ^{**}		0.056

CI: Confidence interval

[‡]Risk factors that were associated with both complications and single-stage endoscopic stone removal in univariate analysis: indication for ERCP and biliary stent placement were included.[§]Procedure-related risk factors associated with complications in previous studies: endoscopist's experience, sphincterotomy technique, pancreatic injection, chemo-prevention, pancreatic stent placement, and antibiotics were included.^{**}Patient-related risk factors associated with complications in previous studies: age, sex, coexisting illness, serum bilirubin, diameter of common bile duct, stone size, stone number, gallstones, and gallbladder were included.

single-stage endoscopic stone removal, indication for ERCP, pancreatic injection, time of deep cannulation, serum bilirubin, and biliary stent placement. Sphincterotomy technique and pancreatic stent placement showed a tendency towards a significant association ($p=0.0501$ and $p=0.056$, respectively). The p values of the other factors were >0.20 . Although single-stage endoscopic stone removal was found to be a significant risk factor for PEP in the univariate analysis ($p=0.014$), it was not significant in the multivariate analysis ($p=0.10$). The propensity score analysis also showed that this procedure was not a significant risk factor for PEP ($p=0.088$).

The incidence of complications associated with a longer deep cannulation time

We next determined whether the deep cannulation time during single-stage endoscopic stone removal was a significant risk factor for complications. Among the 27 patients who underwent single-stage endoscopic stone removal, 8 pa-

tients (29.6%) had complications. Among the 82 patients who underwent two-stage endoscopic stone removal, 9 patients (11.0%) had complications. Among the patients in whom >10 min was required for deep cannulation, three significant factors were identified by the univariate analysis: single-stage endoscopic stone removal, indication for ERCP, and biliary stent placement. The p values for serum bilirubin and pancreatic injection were $p=0.18$ and $p=0.12$, respectively. All other factors had p values of >0.20 . In the multivariate analysis, single-stage endoscopic stone removal was not a significant risk factor for complications ($p=0.70$). The propensity score analysis revealed that single-stage endoscopic stone removal was not a significant risk factor in patients in whom >10 min was required for deep cannulation (Table 5).

The incidence of PEP associated with a longer deep cannulation time

Among the patients in whom >10 min was required for

Table 6. The Number of ERCP Attempts between Single-stage Endoscopic Stone Removal and Two-stage Endoscopic Stone Removal.

Number of ERCP attempts	Single-stage endoscopic stone removal	Two-stage endoscopic stone removal	p value
1	80/114 (70.2%)	15/231 (6.5%)	<0.0001
2	30/114 (26.3%)	183/231 (79.2%)	
3	4/114 (3.5%)	28/231 (12.1%)	
4	0/114 (0%)	4/231 (1.7%)	
5	0/114 (0%)	1/231 (0.43%)	

ERCP: endoscopic retrograde cholangiopancreatography

Table 7. The Hospital Stay between Single-stage Endoscopic Stone Removal and Two-stage Endoscopic Stone Removal.

Hospital stay	Single-stage endoscopic stone removal	Two-stage endoscopic stone removal	p value
≤ 7 days	61/108 (56.5%)	31/223 (13.9%)	<0.0001
≥ 8 days	47/108 (43.5%)	192/223 (86.1%)	

deep cannulation, 8 of the 27 patients (29.6%) who underwent single-stage endoscopic stone removal had PEP. Among the 82 patients with two-stage endoscopic stone removal, 4 patients (4.9%) had PEP. Three factors were found to be significant in the univariate analysis: single-stage endoscopic stone removal, indication for ERCP, and biliary stent placement. Serum bilirubin and sex showed p values of 0.065 and 0.13, respectively; the other factors had p values of >0.20. Although single-stage endoscopic stone removal was a significant risk factor for PEP in the univariate analysis ($p=0.0014$). This procedure did not remain a significant risk factor for PEP in the multivariate analysis ($p=0.34$). However, the propensity score analysis revealed that single-stage endoscopic stone removal was a significant risk factor for PEP (odds ratio =9.9, $p=0.024$, 95% CI= 1.3-114.3).

The efficacy of single-stage stone endoscopic stone removal

Stone removal was successful in all patients in both single-stage endoscopic stone removal and two-stage endoscopic stone removal groups. The numbers of ERCP attempts in the single-stage endoscopic stone removal and two-stage endoscopic stone removal groups are shown in Table 6. The number of ERCP attempts in the single-stage endoscopic stone removal group was significantly lower than that in the two-stage endoscopic stone removal group. In the single-stage endoscopic stone removal group, the proportion of patients with a hospital stay of within 7 days was significantly higher than that in the two-stage endoscopic stone removal group (Table 7). Regarding the analysis of the hospital stay, the cases in which ERCP was performed because choledocholithiasis was observed during hospitalization for other diseases were excluded because the length of hospital stay in association with choledocholithiasis could not be as-

sessed.

Discussion

In the present study, we retrospectively examined the incidence of complications for single-stage endoscopic stone removal, with adjustment for confounding factors using a propensity score analysis. Our results indicated that single-stage endoscopic stone removal was not a risk factor for overall complications, even in patients in whom >10 min was required for deep cannulation.

Several previous studies describing the risk factors and complications associated with ERCP reported that the incidence of complications ranged from 5% to 10%, with PEP, which occurred in 2-7% of the patients, being the most common complication (11-17). In the guidelines published by the American society for gastrointestinal endoscopy in 2017 (2) and by the European society of gastrointestinal endoscopy in 2014 (18), single-stage endoscopic stone removal is not listed as a procedure-related risk factor for complications such as PEP, cholangitis, bleeding, and perforation. Thus, single-stage endoscopic stone removal is generally recommended, as shown in the standard framework of ERCP by the ERCP Working Party of the British Society of Gastroenterology.

However, few reports have examined in detail whether single-stage endoscopic stone removal is a risk factor for complications in patients with naive papilla. In a retrospective trial of 11,497 patients (17) and a prospective trial of 1,177 patients (16), endoscopic stone removal was not found to be a risk factor for complications in ERCP. However, these studies included not only patients with naive papilla but also those with a history of ERCP; thus, the risk of single-stage endoscopic stone removal in patients with naive

papilla could not be accurately evaluated.

First, we considered that calculus must be passed through the papilla for its successful endoscopic removal, and that unavoidable mechanical irritation of the papilla with a single-stage procedure might exacerbate papillary edema, leading to increased overall complications and PEP. However, in the present study, the propensity score analysis revealed that single-stage endoscopic stone removal was not a significant risk factor for overall complications or PEP in patients with naive papilla.

Second, we hypothesized that single-stage endoscopic stone removal may be a risk factor for complications, specifically PEP, in cases of difficult deep cannulation. One of the initial events during pancreatitis involves the blockage of digestive enzyme secretion from pancreatic acinar cells and activation of trypsinogen (19). Clinically, patients undergoing EST or EPBD and those with difficult deep cannulation were found to have a high risk of PEP due to papillary edema (2, 20). In addition to EST and EPBD, many patients in whom >10 min is required to perform deep cannulation may have already developed papillary edema, which could be exacerbated by endoscopic stone removal. Based on a previous study, which reported that patients in whom 10 min was required for deep cannulation had a significantly higher risk of PEP (20), we used 10 min as the cutoff for the duration of deep cannulation in our analyses. After adjustment for confounding factors in the multivariate analysis using propensity scores, it was found that single-stage endoscopic stone removal was not a significant risk factor for overall complications. The propensity score analysis revealed that single-stage endoscopic stone removal was a significant risk factor for PEP in the patients in whom >10 min was required for deep cannulation. However, the analysis of the results on PEP in cases in which >10 min was required for deep cannulation was problematic because only 12 patients suffered from PEP among the 109 patients in whom >10 min was required for deep cannulation. As a result of the small sample size, the 95% CI was very wide.

Although EPLBD was performed recently for patients with large CBDs, the present study only included 3 patients who underwent EPLBD. Some previous studies reported that EPLBD with EST for large CBDs was associated with an equal number (or fewer) ERCP-related complications to EST alone (7, 21). Based on these previous studies, single-stage endoscopic stone removal with EPLBD may be a safe procedure for the removal of large CBDs.

While the safe implementation of single-stage endoscopic stone removal is potentially advantageous due to the associated reductions in medical costs and hospital stay, potential ERCP-associated complications will inadvertently lead to extended hospital stays and increased medical costs, in addition to the increased mental and physical burden on the patients. Furthermore, this negative impact will undoubtedly be exacerbated in cases of severe complications, such as severe PEP. The findings of the present study of patients with naive papilla show that single-stage endoscopic stone removal is

not a significant risk factor for overall complications. Regarding the incidence of PEP, it was not clear whether single-stage endoscopic stone removal was a risk factor of PEP in patients with naive papilla who underwent EST or EPBD because of the small number of patients who suffered from PEP. Single-stage endoscopic stone removal contributed to a reduction in the number of ERCP attempts and a shorter hospital stay.

The present study is associated with several limitations. First, despite adjusting for confounding factors using propensity scores, it is possible that certain confounders contributed to the outcomes as not all potential factors were measured or included in the present study. Second, the analysis of the incidence of PEP in single-stage endoscopic stone removal and two-stage endoscopic stone removal was insufficient because only 16 patients suffered from PEP. Future studies, including randomized controlled trials, should be performed to compare the incidence of complications between single-stage and two-stage endoscopic stone removal.

In summary, we conducted a multivariate analysis using propensity scores to examine the risk of complications associated with single-stage endoscopic stone removal and found that single-stage endoscopic stone removal was not a risk factor for complications in patients with naive papilla who underwent EST, EPBD, or EPLBD. Furthermore, single-stage endoscopic stone removal contributed to a reduction in the number of ERCP attempts and a shorter hospital stay.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We would like to thank the staff at each participating institution for their insightful advice on the planning of the present study, including Drs. Takehiko Koga, Hisashi Itoshima, Masafumi Sakaguchi, Kimitaka Shioya, Kouichi Kudo, Hideto Chikazawa at Saiseikai Kumamoto Hospital; and Tomoyuki Goto, Kazuki Inamura, Norihito Iwasaki, Satoshi Yamabe at Kumamoto City Hospital.

References

1. Maple JT, Ikenberry SO, Anderson MA, et al. The role of endoscopy in the management of choledocholithiasis. *Gastrointest Endosc* **74**: 731-744, 2011.
2. Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. *Gastrointest Endosc* **85**: 32-47, 2017.
3. Ishiwatari H, Kawakami H, Hisai H, et al. Balloon catheter versus basket catheter for endoscopic bile duct stone extraction. *Endoscopy* **48**: 350-357, 2016.
4. Binmoeller KF, Brückner M, Thonke F, Soehendra N. Treatment of difficult bile duct stones using mechanical, electrohydraulic and extracorporeal shock wave lithotripsy. *Endoscopy* **25**: 201-206, 1993.
5. Chang WH, Chu CH, Wang TE, Chen MJ, Lin CC. Outcome of simple use of mechanical lithotripsy of difficult common bile duct stones. *World J Gastroenterol* **11**: 593-596, 2005.
6. Stefanidis G, Christodoulou C, Manolakopoulos S, Chuttani R.

- Endoscopic extraction of large common bile duct stones: A review article. *World J Gastrointest Endosc* **4**: 167-179, 2012.
7. Tsuchida K, Iwasaki M, Tsubouchi M, et al. Comparison of the usefulness of endoscopic papillary large-balloon dilation with endoscopic sphincterotomy for large and multiple common bile duct stones. *BMC Gastroenterol* **15**: 59, 2015.
 8. Kiriya S, Takada T, Strasberg SM, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis. *J Hepatobiliary Pancreat Sci* **20**: 24-34, 2013.
 9. Jorgensen J, Kubiliun N, Law JK. Endoscopic retrograde cholangiography (ERCP): core curriculum. *Gastrointest Endosc* **83**: 279-289, 2016.
 10. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* **37**: 383-393, 1991.
 11. Masci E, Toti G, Mariani A, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* **96**: 417-423, 2001.
 12. Williams EJ, Taylor S, Fairclough P, et al. Risk factors for complication following ERCP: results of a large-scale, prospective multicenter study. *Endoscopy* **39**: 793-801, 2007.
 13. Colton JB, Curran CC. Quality indicators, including complications, of ERCP in a community setting: a prospective study. *Gastrointest Endosc* **70**: 457-467, 2009.
 14. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* **102**: 1781-1788, 2007.
 15. Barthet M, Lesavre N, Desjeux A, et al. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. *Endoscopy* **34**: 991-997, 2002.
 16. Christensen M, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. *Gastrointest Endosc* **60**: 721-731, 2004.
 17. 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* **70**: 80-88, 2009.
 18. Dumonceau JM, Andriulli A, Elmunzer BJ, et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. **46**: 799-815, 2014.
 19. Pezzilli R, Romboli E, Campana D, Corinaldesi R. Mechanisms involved in the onset of post-ERCP pancreatitis. *JOP* **3**: 162-168, 2002.
 20. Wang P, Li ZS, Liu F, et al. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol* **104**: 31-40, 2009.
 21. Yang XM, Hu B. Endoscopic sphincterotomy plus large-balloon dilation vs endoscopic sphincterotomy for choledocholithiasis: a meta-analysis. *World J Gastroenterol* **19**: 9453-9460, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).