

## Endoscopic Retrograde Cholangiopancreatography in Patients with Previous Acute Coronary Syndrome

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**Background/Aims:** Endoscopic retrograde cholangiopancreatography (ERCP) is considered a high-risk procedure in patients with previous acute coronary syndrome (ACS); however, clinical studies are rare in the literature. The aim of this study was to investigate the safety and efficacy of ERCP in patients with previous ACS. **Methods:** We retrospectively reviewed the medical records of patients with previous ACS who underwent ERCP between January 2007 and August 2012. The clinical characteristics, ERCP diagnoses, treatment results, and complications were analyzed. **Results:** Fifty patients underwent ERCP an average of 41.6 months after ACS. The most common indication for ERCP was calculous cholangitis. After deep biliary cannulation, endoscopic sphincterotomy, biliary stone removal and endoscopic biliary drainage were successfully performed. Immediate postsphincterotomy bleeding occurred in seven patients, which was successfully controlled using endoscopic therapy. Elevation of cardiac troponin I levels were observed in three patients (6%) before ERCP, and all of these patients were diagnosed with pancreatobiliary disease combined with recurrent ACS, which was treated with coronary artery stent insertion (n=2) and balloon angioplasty (n=1). **Conclusions:** Therapeutic ERCP is effective and safe in patients with previous ACS. Cardiac troponin I elevation should be considered a warning sign for recurrent ACS in patients who undergo ERCP. (*Gut Liver* 2014;8:674-679)

**Key Words:** Cholangiopancreatography, endoscopic retrograde; Acute coronary syndrome; Troponin I

### INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for various pancreatobiliary disease, including choledocholithiasis, pancreatobiliary malignancy, and postoperative biliary complications.<sup>1-3</sup> Therapeutic ERCP has been shown to lead to less mortality and morbidity than surgery. Although upper gastrointestinal endoscopy and colonoscopy are relatively safe procedures after myocardial infarction (MI),<sup>4-8</sup> ERCP is considered as a high-risk procedure after acute coronary syndrome (ACS).<sup>9-11</sup> ERCP has greater cardiovascular risks than any other endoscopic procedures because of longer procedure time, more anesthetic medications, frequent underlying cholangitis, and frequent need for therapeutic ERCP.<sup>12</sup> Patients with previous ACS (non-ST segment elevation MI, ST segment elevation MI, and unstable angina) are often treated with antiplatelet agents to help restore patency of coronary arteries or to prevent the coronary stent occlusion, but these therapies increase the risk of postsphincterotomy bleeding.<sup>11</sup>

According to English literature, studies about the safety and efficacy of ERCP in patients with previous ACS are rare. The aim of this study was to investigate the efficacy and safety of ERCP in patients with previous ACS.

### MATERIALS AND METHODS

#### 1. Study population

Between January 2007 and August 2012, ERCP was performed in 2,695 patients with pancreatobiliary diseases at Chonnam National University Hospital. Among them, 50 patients with previous history of ACS who had undergone ERCP were included in this retrospective study. The patients' demographic characteristic and clinical data, including age, sex, comorbid

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diseases, medications, symptoms, physical signs, indications for ERCP, and presence of coronary stents were reviewed. Laboratory findings including complete blood cell counts, liver function tests, serum amylase, and cardiac enzymes were reviewed. Clinical outcomes, including treatment results and complications related to ERCP were analyzed. This retrospective study was performed in accordance with the guidelines of our Institutional Review Board.

## 2. Endoscopic procedure

ERCP was performed with a conventional side-viewing duodenoscope in a standard manner. Patients were sedated with midazolam (2.5 to 10 mg) or diazepam (5 to 10 mg), supplemented with pethidine (12.5 to 25 mg) if necessary. All patients received oxygen administered by nasal prong and were monitored by pulse oximetry and electrocardiography. After selective biliary cannulation, therapeutic procedures, such as endoscopic sphincterotomy (EST), stone extraction, and biliary drainage, were performed. EST was performed using a pull-type sphincterotome at the time of the first ERCP in patients who had taken aspirin alone. But, EST was delayed 5 days after discontinuation of clopidogrel in patients who had taken clopidogrel. Without EST, either a 5F to 7F nasobiliary drain (Nasal biliary drainage set; Cook Endoscopy, Winston-Salem, NC, USA) or a 7F to 10F straight stent (Percuflex biliary drainage stent; Microvasive Endoscopy, Boston Scientific Corp., Natick, MA, USA) was placed in bile duct. With an EST, an endoscopic biliary drainage (EBD) was performed in patients with remnant stones or a high suspicion of remnant stones. After ERCP and biliary drainage, all patients were kept under strict observation and were treated in critical care ward.

## 3. Definition

Non-ST segment elevation MI was defined by elevated serum cardiac enzymes (cardiac troponin I >2 times upper limit of normal) without ST-segment elevation and an affirmative diagnosis by an attending cardiologist.<sup>13</sup> ST segment elevation MI was defined by ST-segment elevation and an affirmative diagnosis by an attending cardiologist.<sup>13</sup> Unstable angina was diagnosed by clinical presentation of new-onset, crescendo, or at-rest angina; ECG changes of ST-segment depression and/or T-wave inversion; and an affirmative diagnosis by an attending cardiologist.<sup>13</sup>

To evaluate ERCP-related complications, complete blood counts, liver enzymes, and serum amylase were measured before and within 4 and 24 hours after ERCP. Post-ERCP pancreatitis was defined as the presence of abdominal pain with post-ERCP amylase elevation.<sup>14</sup> Post-ERCP amylase elevation was defined as the elevation of serum amylase more than three times the normal range and basal level. Significant post-ERCP bleeding was defined as clinical evidence of bleeding with a decrease in

hemoglobin of more than 2 g/dL.<sup>14</sup> Immediate postsphincterotomy bleeding was defined as bleeding that occurred at the time of sphincterotomy.<sup>15</sup> Delayed postsphincterotomy bleeding was defined as bleeding that occurred after the end of the ERCP procedure.<sup>15</sup>

## 4. Statistical analysis

All statistical analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL, USA).

Fisher exact test and Mann-Whitney U test were used for statistical analyses where appropriate. Mann-Whitney U test was used for continuous variables that appeared to have a skewed distribution and Fisher exact test was used when appropriate for the comparison of categorical variables. Statistical significance was defined as a p-value less than 0.05.

## RESULTS

### 1. Demographic characteristics

During the study period, 50 patients with previous ACS underwent ERCP. There were 30 men and 20 women with a mean age of 72.5±8.3 years. Their mean interval from coronary angiogra-

**Table 1.** Demographic and Clinical Characteristics

Characteristic	Value
No. of patients	50
Age, yr	72.5±8.3 (51–86)
Male/Female	30/20
Interval from CAG to ERCP, mo	41.6±46.1 (0–208)
Comorbidity	
Cerebrovascular accident	7 (14)
Previous coronary stent insertion	26 (52)
Previous biliary stone (GB stone/CBD stone/Both)	25 (1/7/17) (50)
Antiplatelet agents	
None	3 (6)
Aspirin monotherapy	22 (44)
Clopidogrel monotherapy	3 (6)
Aspirin+Clopidogrel dual therapy	22 (44)
Symptoms	
Fever	21 (42)
Abdominal pain	38 (76)
Biliary pain	28 (56)
Chest pain	8 (16)
Jaundice	16 (32)
Charcot's triad	10 (20)

Data are presented as mean±SD (range) or number (%). CAG, coronary angiogram; ERCP, endoscopic retrograde cholangiopancreatography; GB, gallbladder; CBD, common bile duct.

phy to ERCP was  $41.6 \pm 46.1$  months. Twenty-six patients (52%) had one or more coronary stents. The baseline demographic and clinical characteristics of the patients were summarized in Table 1. Thirty-eight patients (76%) suffered from abdominal pain, and 28 patients (56%) showed typical biliary pain.

## 2. Laboratory results, diagnosis, and therapeutic ERCP outcomes

Laboratory results, diagnosis, and therapeutic ERCP outcomes were summarized in Table 2. The most common indication for ERCP was calculous cholangitis (41, 82%). Forty-nine patients (98%) underwent successful cannulation. After deep biliary cannulation, endoscopic sphincterotomy (35, 70%), biliary stone removal (39, 78%), and EBD (30, 60%) were successfully performed.

Elevation of cardiac troponin I was observed in three patients (6%) before ERCP. Three patients with elevation of cardiac troponin I were all diagnosed as a pancreatobiliary disease combined with recurrent ACS which was confirmed by coronary angiography. One 81-year-old man with elevation of cardiac troponin I and abdominal pain underwent coronary angiography with plain old balloon angioplasty for left circumflex artery stenosis at arrival and succeeded in ERCP without EST for CBD

**Table 2.** Laboratory Results, Diagnosis, and Therapeutic Endoscopic Retrograde Cholangiopancreatography Outcomes

Variable	Value
Laboratory findings	
White blood cell, /mm <sup>3</sup>	10,340 $\pm$ 5,730
Platelet, /mm <sup>3</sup>	215,000 $\pm$ 74,000
Prothrombin time, INR	1.07 $\pm$ 0.11
Activated partial thromboplastin time, sec	35.40 $\pm$ 7.01
Troponin I, ng/mL	0.29 $\pm$ 1.57
Elevation of cardiac troponin I	3 (6)
Diagnosis	
Calculous cholangitis	41 (82)
Periampullary malignancy	6 (12)
Cholecystitis	2 (4)
Pancreatitis	1 (2)
Therapy	
No. of ERCP session	1.3 $\pm$ 0.5
Successful biliary cannulation	49 (98)
Endoscopic sphincterotomy	35 (70)
EBD	30 (60)
Stone removal	39 (78)

Data are presented as mean $\pm$ SD or number (%).

INR, international normalized ratio; ERCP, endoscopic retrograde cholangiopancreatography; EBD, endoscopic biliary drainage.

stone removal. The other 71-year-old man underwent ERCP and stone removal successfully, but cardiac troponin I gradually elevated. He underwent stent insertion for right coronary artery total occlusion 8 days after ERCP and underwent new stent insertion for the treatment of in-stent restenosis in left anterior descending coronary artery 10 days after ERCP. Another 71-year-old woman underwent coronary angiography with plain old balloon angioplasty for the treatment of in-stent restenosis in right coronary artery 8 days after ERCP.

## 3. Complications related to ERCP

Thirty-nine patients didn't have any complications after ERCP. Mild post-ERCP pancreatitis was occurred in six patients, and they recovered uneventfully. Immediate postsphincterotomy bleeding was occurred in seven patients. Primary hemostasis was successfully achieved with endoscopic therapy including balloon compression and epinephrine injection. One patient (2%) with multiple coronary stents expired 3 days after ERCP due to delayed postsphincterotomy bleeding and ischemic cardiac injury. Complications related to ERCP were summarized in Table 3.

Among 50 patients, EST was performed in 35 patients. Seventeen patients were taking an antiplatelet agent (monotherapy group, aspirin or clopidogrel) and 18 patients were taking two antiplatelet agents (dual therapy, aspirin with clopidogrel). Immediate and delayed postsphincterotomy bleeding rates were not significantly different between mono- and dual therapy group (Table 4).

**Table 3.** Complications Related to Endoscopic Retrograde Cholangiopancreatography

Complication	No. (%)
None	39 (78)
Abdominal pain	4 (8)
Post-ERCP pancreatitis	6 (12)
Immediate bleeding	7 (14)
Delayed bleeding	1 (2)
Death	1 (2)

ERCP, endoscopic retrograde cholangiopancreatography.

**Table 4.** Postsphincterotomy Bleeding according to the Use of Antiplatelet Agents

	EST (n=35)	Monotherapy (n=17)	Dual therapy (n=18)	p-value
Immediate bleeding		2 (11.8)	5 (27.8)	0.402
Delayed bleeding		0	1 (5.6)	1.000

Data are presented as number (%).

EST, endoscopic sphincterotomy.

**Table 5.** Clinical Characteristics, Therapeutic Results, and Complications according to the Interval from Coronary Angiogram to Endoscopic Retrograde Cholangiopancreatography

Variable	≤6 mo (n=12)	>6 mo (n=38)	p-value
Age, yr	73.0±9.6	72.4±8.0	0.617
Sex, male/female	6/6	24/14	0.506
MI/unstable angina	3/9	14/24	0.510
Antiplatelet agents			
None	0	3 (7.9)	1.000
Aspirin monotherapy	4 (33.3)	18 (47.4)	0.512
Clopidogrel monotherapy	1 (8.3)	2 (5.3)	1.000
Aspirin+Clopidogrel dual therapy	7 (58.3)	15 (39.5)	0.324
Elevation of cardiac troponin I	1 (8.3)	2 (5.3)	1.000
Therapy			
Successful biliary cannulation	12 (100)	37 (97.4)	1.000
Endoscopic sphincterotomy	7 (58.3)	28 (73.7)	0.471
EBD	9 (75.0)	21 (55.3)	0.317
Stone removal	12 (100)	37 (97.4)	1.000
Complications			
Abdominal pain only	0	4 (10.5)	0.560
Post-ERCP pancreatitis	3 (25.0)	10 (26.3)	1.000
Immediate bleeding	3 (25.0)	4 (10.5)	0.337
Delayed bleeding	1 (8.3)	0	0.240
Death	1 (8.3)	0	0.240

Data are presented as mean±SD or number (%).

MI, myocardial infarction; EBD, endoscopic biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography.

Follow-up cardiac enzyme levels after ERCP were checked in 15 patients and it showed no significant interval change compared with initial troponin I levels (0.80±2.67 vs. 0.63±1.99,  $p=0.313$ ). Other patients had no clinical evidence of ACS after ERCP, so they didn't check the follow-up cardiac enzymes.

#### 4. Clinical characteristics, ERCP outcomes, and complications related to ERCP according to the interval from coronary angiography to ERCP

Clinical characteristics, therapeutic ERCP outcomes, and complications related to ERCP according to the interval from coronary angiography to ERCP were summarized in Table 5. There was no significant difference in therapeutic ERCP outcomes between two groups. And, there was no significant difference in complications related to ERCP between two groups. Postsphincterotomy bleeding rates were not significantly different between two groups.

## DISCUSSION

Although ERCP is considered as a high-risk procedure after ACS,<sup>9-11</sup> studies about the safety and efficacy of ERCP in patients with previous ACS are rare. A study reported that therapeutic ERCP involved acceptable risks when performed soon after MI or unstable angina, but the study didn't include the patients with coronary stents.<sup>11</sup> The present study included 26 patients with coronary stent for the treatment of previous ACS. And, the present study also included 22 patients with dual antiplatelet agents for the treatment of previous ACS. In the present study, therapeutic ERCP procedures including endoscopic sphincterotomy, biliary stone removal, and endoscopic biliary drainage were successfully performed in all patients after deep biliary cannulation (49/50, 98%).

The patients with coronary stent might be vulnerable to myocardial ischemia during ERCP. Experimental studies performed in the last decade indicate that inflammatory mechanisms play a key role in the process of neointimal proliferation and restenosis of the coronary stent.<sup>16</sup> Most of the patients with pancreatobiliary disease might have systemic inflammation enough to stimulate restenosis of the coronary stent. In the present study, three patients showed combined diseases with acute calculous cholangitis and recurrent ACS. Among them, two patients showed restenosis of the coronary stent. One patient underwent new stent insertion and the other underwent plain old balloon angioplasty for the treatment of restenosis of the coronary stent. Systemic inflammation by acute calculous cholangitis might play a role in restenosis of the coronary stent. And, most of the patients with coronary stents had dual therapy with aspirin and clopidogrel to prevent coronary stent occlusion, which increased the risk of postsphincterotomy bleeding resulting systemic hypotension and myocardial ischemia. In the present study, one patient with multiple coronary stents expired 3 days after ERCP due to postsphincterotomy bleeding and ischemic cardiac injury.

After ACS regardless of coronary stent insertion, patients take one or more than one antiplatelet agent. It tends to make a higher bleeding tendency during ERCP procedure including sphincterotomy. There is a wide variation of postsphincterotomy bleeding rates based on the variable definition of postsphincterotomy bleeding.<sup>15</sup> The incidence of immediate postsphincterotomy bleeding was around 10%, respectively.<sup>15</sup> In the present study, the incidence of immediate postsphincterotomy bleeding was 14% in all patients, which was comparable to the reported range. However, immediate postsphincterotomy bleeding rate was 27.8% in patients with dual therapy of aspirin and clopidogrel despite 5-day discontinuation of clopidogrel. All cases of immediate postsphincterotomy bleeding were successfully controlled with endoscopic treatment including balloon compression and injection therapy in the present study. And, clinically

significant delayed postsphincterotomy bleeding was occurred in one of the patients (5.6%) with dual therapy. The current results suggested that dual therapy with aspirin and clopidogrel might be considered as a risk factor for postsphincterotomy bleeding. It is necessary that prospective studies with a large number of patients should be performed to prove the clinical significance of dual therapy for immediate and delayed postsphincterotomy bleeding.

In the literature, the reported incidence of post-ERCP pancreatitis ranges from 1% to 18%.<sup>17</sup> In the present study, the incidence of post-ERCP pancreatitis was 12%. All patients with post-ERCP pancreatitis recovered uneventfully. Among three patients with acute cholangitis and ACS, two patients (66%) underwent ERCP at first and succeeded in coronary angiography. Both of them experienced post-ERCP pancreatitis. However, the other patient underwent coronary angiography at first and succeeded in ERCP. He didn't experience post-ERCP pancreatitis. It could be speculated that the patients with ACS might be vulnerable to post-ERCP pancreatitis by reducing blood supply to pancreas. Lee *et al.*<sup>18</sup> also reported that patients with intraprocedural cardiac ischemia were found to have a higher risk of post-ERCP pancreatitis. Although the pathogenic mechanisms responsible are not completely understood, splenic vessel insufficiency and reperfusion injury to the pancreas resulting from myocardial ischemia may play an important role.<sup>18</sup> Ischemia-reperfusion is considered to be a trigger mechanism for distinct types of acute pancreatitis.<sup>19</sup>

In the present study, cardiac troponin I level was elevated in three patients with pancreatobiliary disease and previous ACS. All patients (3/3, 100%) with elevation of cardiac troponin I were diagnosed as recurrence of ACS by coronary artery angiography. Cardiac troponin I was helpful to distinguish combined recurrent ACS in patients with pancreatobiliary diseases. An elevation of cardiac troponin I levels provides an early and highly specific and sensitive diagnosis of a myocardial lesion.<sup>17</sup>

In conclusion, therapeutic ERCP is effective and safe in patients with previous ACS. Elevation of cardiac troponin I should be considered a warning sign for recurrent ACS in patients who undergo ERCP.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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