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Original Article

Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis by Endoscopic Pancreatic Stenting after Insertion of Self-Expandable Metal Stent for Malignant Distal Biliary Stricture

Ryo Harada*, Ryosuke Sato, Tomoaki Tsutsui, Nao Hattori,
Masafumi Inoue, and Haruhiko Kobashi

Department of Gastroenterology and Hepatology, Japanese Red Cross Okayama Hospital, Okayama 700-8607, Japan

The insertion of a self-expandable metal stent (SEMS) for nonpancreatic cancer is a factor predicting the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). We evaluated the efficacy of endoscopic pancreatic stenting (EPS) to prevent PEP after SEMS insertion in patients with malignant distal biliary stricture and without main pancreatic duct (MPD) obstruction. We performed a single-center, retrospective, historically controlled investigation to assess the outcomes of 33 consecutive patients who underwent SEMS insertion. From March 2013 to June 2015, 13 patients did not undergo EPS (Non-EPS group). The other 20 patients underwent EPS (EPS group) between July 2015 and August 2018. The background data demonstrated no significant differences. Except for one patient in the Non-EPS group, all patients underwent biliary sphincterotomy. The EPS group's PEP incidence was significantly lower (n = 1, 5%) than that of the Non-EPS group (n = 4, 31%) ($p = 0.04$). The median serum amylase and lipase levels after the procedure were significantly lower in the EPS group than in the Non-EPS group (amylase: 104 vs. 262 U/L; $p < 0.01$, lipase: 102 vs. 666 U/L; $p = 0.01$). The use of EPS decreased the incidence of PEP after SEMS insertion in individuals with malignant distal biliary stricture and without MPD obstruction.

Key words: post-endoscopic retrograde cholangiopancreatography pancreatitis, endoscopic pancreatic stent, main pancreatic duct obstruction, self-expandable metal stent, distal biliary stricture

The insertion of a self-expandable metal stent (SEMS) is the first-line option for an unresectable malignant distal biliary stricture. Compared to traditional plastic stents, SEMSs allow for good drainage and high patency rates [1-3]. A SEMS costs more than a plastic stent, but its use results in fewer re-interventions and hospital stays. A SEMS is also a cost-effective palliative treatment for individuals with unresectable diseases [4,5]. However, SEMSs are associated with some serious complications, *e.g.*, cholecystitis, cholangitis, and pancreatitis. Many mechanisms of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) have been suggested; one is main pancreatic duct (MPD) obstruction due to papillary swelling during the procedure [6-10]. In order to solve this problem and prevent PEP, endoscopic pancreatic stenting (EPS) for individuals at high risk of developing PEP is recommended by international guidelines [11-14].

We have performed SEMS insertions for malignant distal biliary strictures with biliary sphincterotomy, and we sometimes observe PEP in patients without MPD obstruction. Shimizu *et al.* and Kawakubo *et al.* revealed that nonpancreatic cancer is a risk factor predicting PEP

after SEMS placement in patients with a distal malignant biliary stricture, because MPD tumor involvement is low and exocrine function is usually preserved in patients with nonpancreatic cancer [15,16]. However, no study has evaluated the efficacy of EPS following SEMS insertion in patients with a distal malignant biliary stricture with nonpancreatic cancer. We have thus introduced the routine use of EPS following SEMS insertion in individuals with a distal biliary stricture without MPD obstruction, with the goals of preventing the SEMS from compressing the MPD and of decreasing PEP risk. We performed the present investigation to determine the efficacy of EPS for the prevention of PEP after SEMS insertion in patients without MPD obstruction.

Patients and Methods

Patients. All of the patients in this study were identified from our endoscopic retrograde cholangiopancreatography (ERCP) database. Between March 2013 and August 2018, 83 patients underwent a SEMS insertion for a distal biliary stricture. All of these patients underwent an examination including a computed tomography (CT) scan and/or magnetic resonance imaging before undergoing the ERCP. By using the findings of those examinations, we excluded patients with MPD obstruction and/or dilatation of the MPD > 4 mm (n = 38). Patients with a history of SEMS insertion (n = 9) and patients with a benign biliary stricture (n = 3) were excluded as well. We thus retrospectively investigated the cases of 33 patients.

Of the 33 patients, 13 underwent a SEMS insertion between March 2013 and June 2015 and did not undergo the insertion of a pancreatic stent (Non-EPS group). The other 20 patients who underwent SEMS insertion between July 2015 and August 2018 underwent a pancreatic stent insertion (EPS group) (Fig. 1). These two periods were mutually exclusive. The Ethics Committee of our institute approved the study design (Japanese Red Cross Okayama Hospital, 2018-84), and the study adhered to the Declaration of Helsinki. Before each ERCP, the patient provided written informed consent to undergo the procedure and for the data to be used.

SEMS procedures. The deployed stent was a 5-French straight pancreatic stent with various lengths (3-7 cm) (Geenen: Cook Endoscopy, Winston-Salem,
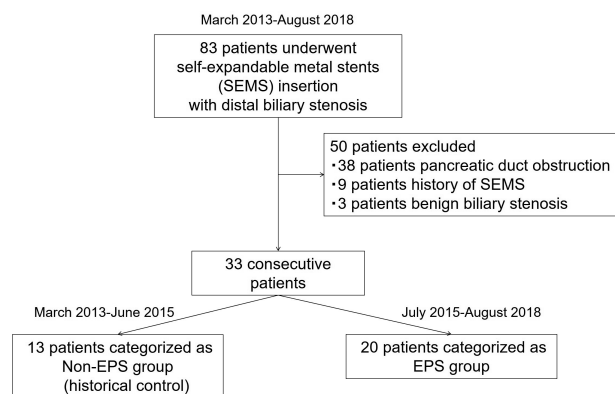

Fig. 1   Trial profile.

NC, USA). Four SEMS were used: WallFlex (Boston Scientific; Natick, MA, USA); X-Suit NIR (Olympus; Tokyo); BONA Stent (Medicos-Hirata; Osaka, Japan); and Niti-S (Taewoong Medical; Seoul, Korea). Each ERCP was conducted with a JF-260V or TJF-260V video endoscope (Olympus Medical; Tokyo) with the patient under conscious sedation (midazolam, pethidine hydrochloride). Selective MPD or common bile duct cannulation was first attempted using an ERCP Catheter (MTW Endoscopie; Wesel, Germany) and a 0.025-inch guidewire (VisiGlide or VisiGlide2: Olympus Medical Systems, Tokyo). A guidewire-assisted cannulation technique was attempted as the first option; if this proved difficult, a more conventional contrast-assisted cannulation method was used. After biliary cannulation, the guidewire was passed through the biliary stricture and then placed in the intrahepatic bile duct. A sphincterotomy with a moderate incision was achieved with a blended current. A moderate incision was defined as one that exceeded the transverse fold and did not reach the superior margin of the papillary bulge, according to the Japan Gastroenterological Endoscopy Society guidelines for endoscopic sphincterotomy [17]. The SEMS was then inserted over the guidewire by using a fluoroscopic control.

In the EPS group, generally, the patients were cannulated by the double-guidewire method in biliary cannulation. If pancreatic cannulation proved difficult, we cannulated to a pancreatic duct after a biliary sphincterotomy or a precut papillotomy. The pancreatic stent was inserted (under fluoroscopic control) over the guidewire before the SEMS insertion (Fig. 2). In the Non-EPS group, we tried not to cannulate MPD and completed the procedure without EPS. If the ERCP training fellow
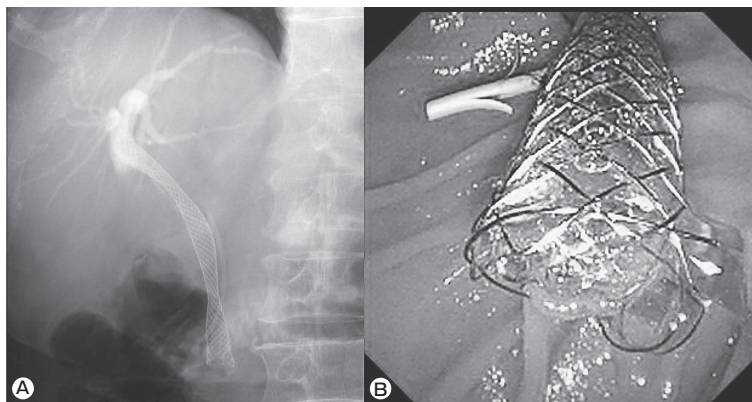
Fig. 2 Placement of pancreatic stent and fully covered metal stent. **A**, Fluoroscopic imaging; **B**, Endoscopic imaging.

could not obtain an endoscopic retrograde pancreatography (ERP) or endoscopic retrograde cholangiography (ERC) image within 10 min, two senior endoscopists with a total career length of more than 10 years and experience with 2,000 ERCPs helped obtain the ERP or ERC image. When it took longer than 10 min to achieve a successful selective cannulation, the procedure was categorized as difficult.

The stent type was chosen by the operator to achieve the safest and most successful procedure. The pancreatic stent was not removed unless and until it clogged and caused pancreatitis. We infused 150,000 U of ulinastatin (Mochida Pharmaceutical, Tokyo, Japan) dissolved in 100 mL of 0.9% saline solution immediately after the ERCP throughout the study period. In both patient groups, diclofenac was administered at the discretion of each endoscopist. We defined 'adverse events' in accord with the lexicon of endoscopic adverse events issued by the American Society Gastrointestinal Endoscopy [18]; ERCP-related adverse events were defined in accord with the European Society of Gastrointestinal Endoscopy Guideline [11].

Definitions of post-ERCP pancreatitis. We defined 'PEP' based on the standard criteria [11]: new abdominal pain or worsening abdominal pain persisting for ≥24 h after the ERCP, in addition to a serum amylase level or a serum lipase level >3 times the upper limit of normal. We also graded pancreatitis according to the standard criteria [11]: 'mild', no organ failure and no local or systemic complications; 'moderate', transient (<48 h) organ failure and/or local or systemic complications without persistent organ failure; and 'severe', persistent (48 h) organ failure.

Statistical analysis. The study's primary endpoint was the development of PEP. We compared categorical variables and continuous variables between the EPS and Non-EPS groups by using the χ^2 test and the Mann-Whitney U-test. P-values < 0.05 were accepted as significant. All statistical analyses were conducted using the JMP ver. 12.2.0 statistical software package (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and procedures. The background data demonstrated no significant between-group differences (Table 1). In both groups, the primary diseases included pancreatic cancer, biliary cancer, gastric cancer, and colon cancer. One ovarian cancer was included in the EPS group. Four patients (20%) in the EPS group and 4 (31%) in the Non-EPS group were given analgesic drugs for abdominal pain before ERCP. Fifteen patients (75%) had naïve papilla in the EPS group, as did 6 (46%) in the Non-EPS group ($p = 0.14$). In the EPS group, pancreatography was performed in all patients for the deployment of the pancreatic stents, whereas only 6 (46%) patients in the Non-EPS group underwent pancreatography ($p < 0.01$). In the Non-EPS group, only one patient did not undergo biliary sphincterotomy and 2 patients underwent insertion of uncovered SEMS. Regarding the marker for procedure difficulty, more than 10 min elapsed for successful selective cannulation in 4 patients (20%) in the EPS group and in 3 patients (23%) in the Non-EPS group (Table 2). EPS was successful in all 20 patients in the EPS group.

Pancreatitis, hyperamylasemia, and serum levels of amylase and lipase.   One of the 20 EPS patients (5%) and 4 of the 13 Non-EPS patients (31%) developed PEP ($p = 0.04$) (Table 3). The one EPS group patient who developed moderate PEP. However, all cases of PEP resolved with conservative therapy without SEMS removal. There was no significant between-group difference in the incidence of hyperamylasemia ($p = 0.11$).

Table 1   Baseline characteristics of the patients

	EPS (n = 20)	Non-EPS (n = 13)	p-value
Mean age, year (range)	80 (67–95)	74 (45–90)	0.37
Males/Females	13/7	9/4	0.99
Primary disease (Pancreatic cancer/Biliary cancer/Gastric cancer/Colon cancer/Ovarian cancer)	4/10/1/4/1	3/6/3/1/0	0.46
Administration of analgesic drugs for abdominal pain	4 (20%)	4 (31%)	0.68
Previous post ERCP pancreatitis	0	1	0.39
Mean main pancreatic duct dia., mm (range)	2.4 (1–4)	2.0 (1–4)	0.23
Administered diclofenac	3 (15%)	2 (15%)	0.98
Observation period, days; median (IQR)	159 (85–373)	231 (35–283)	0.47

ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range.

Table 2   ERCP findings and endoscopic procedure

|	EPS (n = 20)	Non-EPS (n = 13)	p-value
Naïve papilla	15 (75%)	6 (46%)	0.14
Duodenal diverticulum	1 (5%)	1 (8%)	0.75
Previous biliary plastic stent	5 (25%)	7 (54%)	0.14
Pancreatography	20 (100%)	6 (46%)	<0.01
Precut*	2 (10%)	1 (8%)	0.82
Biliary sphincterotomy	20 (100%)	12 (92%)	0.40
More than 10 minutes elapsed for the successful selective cannulation	4 (20%)	3 (23%)	0.99
Mean procedure time, min (range)	28 (15–36)	30 (16–73)	0.46
Trainee participation	8 (40%)	3 (23%)	0.31
Stent type (covered/uncovered)	20/0	11/2	0.15

*Precut include precut papillotomy and transpancreatic sphincterotomy.
ERCP, endoscopic retrograde cholangiopancreatography.

Table 3   Incidence of pancreatitis and hyperamylasemia and serum levels of amylase and lipase

	EPS (n=20)	Non-EPS (n = 13)	p-value
Pancreatitis	1 (5%)	4 (31%)	0.04
Mild	0	4	
Moderate	1	0	
Severe	0	0	
Hyperamylasemia	3 (15%)	7 (54%)	0.11
Serum amylase, U/L; median (IQR)			
Before	72 (40–84)	65 (55–94)	0.52
18 h after procedure	104 (54–169)	262 (147–1,392)	<0.01
Serum lipase, U/L; median (IQR)			
Before	42 (20–75)	62 (28–101)	0.63
18 h after procedure	102 (33–216)	666 (134–1,850)	0.01

IQR, interquartile range.
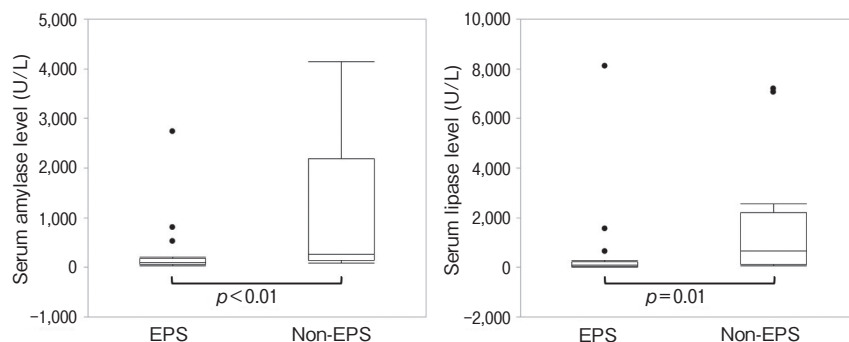
Fig. 3   Comparison of serum amylase and lipase levels between EPS and Non-EPS groups after endoscopic retrograde cholangiopancreatography. Both serum amylase and lipase levels were significantly lower in the EPS group than in the Non-EPS group ($p < 0.01$, $p = 0.01$, respectively).

The median serum amylase level and the median serum lipase level at 18 h after the procedure were both significantly lower in the EPS group than in the Non-EPS group (amylase: 104 vs. 262 U/L; $p < 0.01$, lipase: 102 vs. 666 U/L; $p = 0.01$) (Table 3, Fig. 3).

Other complications.   No other major early complications were observed. SEMS dislodgement was observed after approx. 18 months in one EPS group patient. Mild pancreatitis was observed in one EPS group patient after 1 month, but this resolved with conservative therapy and without the need for pancreatic stent extraction.

Discussion

A biliary SEMS is the first option for an unresectable malignant distal biliary stricture. Previous studies showed a comparatively high frequency of acute adverse events caused by mechanical stent compression, such as cholecystitis and pancreatitis [15,16,19]. Some cases of pancreatitis have required the immediate removal of a stent after its insertion. Itoi *et al.* reported the case of a patient with lethal PEP after SEMS insertion in a distal biliary stricture due to unresectable cholangiocarcinoma [20]; the SEMS was removed just 2 days after the procedure. However, the PEP worsened and the patient died. Itoi *et al.* suggested 2 major mechanisms of PEP after SEMS insertion. One is MPD opacification during the ERCP procedure: namely, common PEP. The other mechanism is impaired drainage from the MPD due to SEMS compression toward the papilla. Based on their patient's clinical course, Itoi *et al.* concluded that the expansive force of the SEMS caused the patient's PEP.

The present report is the first to reveal that using EPS decreased the rate of PEP in individuals without MPD obstruction, even though all 20 of the patients in the EPS group underwent pancreatography. This may support the theory that MPD obstruction caused by the expansive force of the SEMS is the most important factor for PEP after the insertion of a SEMS in a distal biliary stricture.

Shimizu *et al.* and Kawakubo *et al.* revealed that nonpancreatic cancer was one of the predictive risk factors for PEP after SEMS insertion in a distal biliary stricture [15,16]. Isayama *et al.* and Nakai *et al.* showed that the rate of PEP in individuals with MPD obstruction by their tumors was low [21,22]. Usually, most patients with pancreatic head cancer also show MPD involvement by the tumor, and the pancreatic parenchyma of the distal part is atrophic. They thus have impaired exocrine function. However, in patients with nonpancreatic cancer, the MPD is not completely obstructed and exocrine function of the pancreas is preserved. In accord with this theory, we conducted the present study with patients without MPD obstruction.

Insertion to a pancreatic duct is sometimes difficult, and a failure in pancreatic duct cannulation presents a risk of PEP. In our patient series, EPS was successfully inserted in all EPS group patients. Fifteen patients were cannulated to the pancreatic duct first; one patient required a precut papillotomy and 4 required a biliary sphincterotomy for cannulation into the pancreatic duct. It is widely known that cannulation after a biliary sphincterotomy is a comparatively easy way to cannulate a pancreatic duct. After a biliary sphincterotomy, it is easy to identify the pancreatic duct.

Mild pancreatitis as a late complication was observed in only one of our EPS group patients (at ~ 1 month after the procedure), and it resolved with conservative therapy and without the removal of the pancreatic stent. The reason why other patients did not have pancreatitis is unknown. We speculate that because the 5-Fr pancreatic stent is thin, pancreatic juice could leak out through the peripheral space around the pancreatic stent. Late adverse events are an important concern with this method, and careful observation of these patients is necessary. However, it may be easy to exchange a pancreatic stent because we can easily identify the pancreatic duct orifice after pancreatic stent extraction. When there is no pancreatic stent, it might be difficult to find the pancreatic duct orifice after SEMS placement.

Our study has some limitations. The number of patients was relatively low, and the study design was retrospective. Due to the small number of patients, it may not be possible to conclude whether EPS can prevent PEP in patients without MPD obstruction. Second, the imaging confirmation of PEP was not done by CT scan due to our investigation's retrospective design. The abdominal pain associated with PEP can be difficult to distinguish from the abdominal pain related to SEMS expansion. We used standard criteria: abdominal pain lasting ≥ 24 h and a high level of serum amylase or serum lipase. Abdominal pain may include the pain associated with stent expansion. We therefore also compared the serum amylase and lipase levels in both groups. Third, the PEP rate in the Non-EPS patients was high (31%), but this value is similar to the 28% in another study of nonpancreatic cancer patients [15].

In summary, our analyses demonstrated that the PEP incidence was reduced and the serum amylase and serum lipase levels 18 h post-ERCP were lower in EPS patients than in non-EPS patients. The use of EPS decreased the rate of PEP in patients without MPD obstruction after the insertion of a SEMS. Although additional studies with larger numbers of patients and prospective randomized controlled studies are needed, we recommend the use of endoscopic pancreatic stenting before SEMS insertion in patients without MPD obstruction for the prevention of PEP.

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