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의학석사 학위논문

Increasing Number of Pancreatic Duct
Cannulation Attempts Beyond One and
Metal Biliary Stent Insertion as Risk Factors
for Post-Endoscopic Retrograde
Cholangiopancreatography Pancreatitis

2 회 이상의 췌관 삽관과 금속 담도 스텐트 삽입이
내시경 역행담췌관조영술 후 발생하는 췌장염에
미치는 영향

울산대학교 대학원

의 학 과

신 승 환

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Cholangiopancreatography Pancreatitis

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이 논문을 의학박사 학위 논문으로 제출함

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ABSTRACT

Background and Aims: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a major complication of ERCP; in severe cases, it can be life threatening. Many PEP risk factors, including pancreatic duct cannulation, have been identified; however, whether the number of repeat cannulation attempts affects PEP risk is unknown. We aimed to identify the effects of repeated pancreatic duct cannulation and other potential risk factors on PEP incidence.

Methods: We retrospectively analyzed 877 patients with native papillae who underwent ERCP, at Asan Medical Center between January 2012 and December 2016. We examined potential patient- and procedure-related risk factors, and PEP incidence by univariable and multivariable logistic regression analyses.

Results: The most common indication for ERCP was the presence of pancreatobiliary stones/sludge (47.8%), followed by pancreatobiliary malignancy (37.4%). Thirty-four patients (3.9%) had mild (21 patients; 2.4%), moderate (12 patients; 1.4%), and severe (one patient; 0.1%) PEP. Univariable analysis revealed younger age, diagnosis of malignant common bile duct or ampulla of Vater stricture, two or more episodes of pancreatic duct cannulation, and metal biliary stent insertion as risk factors and pancreatobiliary stones/sludge as a protective factor for PEP. Following multivariable analysis, two or more episodes of pancreatic duct cannulation and metal biliary stent insertion remained in the final model. PEP did not increase significantly in case of a single cannulation (4.0%) compared with no cannulation (2.7%). However, patients with two cannulations had 8.0% incidence; those with three or more cannulations had 14.3% incidence.

Conclusions: Pancreatic duct cannulation and metal biliary stent insertion were associated with increased PEP incidence in patients undergoing ERCP performed by highly experienced endoscopist. As for the pancreatic duct cannulation, two or more cannulations considerably increased PEP incidence. This suggested that preventive measures, such as pancreatic duct stent placement or rectally administered nonsteroidal anti-inflammatory drugs or alternative cannulation measures might be considered in patients with two or more cannulations or those undergoing metal biliary stent insertion.

Keywords: ERCP, Post-ERCP pancreatitis, pancreatic duct cannulation, metal biliary stent

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INTRODUCTION

In recent decades, endoscopic retrograde cholangiopancreatography (ERCP) has become an important procedure for patients with pancreatobiliary disease. ERCP plays diverse roles from diagnosis to therapeutic interventions. Despite its development within various procedure tools and techniques, post-ERCP complications continue to be associated with unfavorable outcomes. Among these, post-ERCP pancreatitis (PEP) is relatively common, with an incidence of 1.6% - 15.1%^(1,2) and most large-scale, prospective studies reporting incidences of 3% - 6%.⁽³⁻⁶⁾ Most cases are mild to moderate, but 11.4% of cases are severe that require hospitalization for ≥ 10 days or have PEP combined with complications requiring surgical or radiologic interventions. In one meta-analysis of many prospective studies, the mortality rate was 3.08%.⁽⁶⁾ It is important to identify PEP risk factors in advance and predict its occurrence and, if needed, take preventive measures. Many studies have attempted to identify these risk factors and have divided the known risk factors into three categories: patient-, endoscopist-, and procedure-related risk factors.⁽⁷⁾ Of these, procedure-related risk factors are important because endoscopists can predict PEP during or after the procedure and can stop the procedure, change to an alternative procedure, or take preventive measures for PEP.

Difficult cannulations that require multiple cannulation attempts and pancreatic duct opacification are well known and important procedure-related risk factors for PEP that have been identified in many previous studies.^(2-5, 8-11) In recent studies, pancreatic duct cannulation has been identified as an independent risk factor for PEP even without multiple cannulation attempts or pancreatic duct opacification.^(5, 10, 12, 13) Pancreatic duct cannulation is usually performed to generate a diagnostic pancreatogram or as a therapeutic intervention for the pancreas; however, many pancreatic duct cannulations are performed unintentionally while performing duct cannulation. Consequently, it is important to know that pancreatic duct cannulation is a risk factor for PEP and develop preventive methods or reduce the chance of unintended cannulation. When performing the pancreatic duct cannulation regardless of intention, it is important to understand that PEP risk increases with each cannulation. The cut-off value for PEP risk based on the pancreatic duct cannulation number is also important, in addition to the cannulation event itself. Previous studies focused on pancreatic duct

cannulation as a risk factor for PEP, yet did not determine a cut-off value or increasing PEP incidence in patients undergoing ERCP.

This study aimed to describe the proportionally increasing relationship that exists between pancreatic duct cannulation number and PEP incidence and determine the cut-off value for PEP risk. We also underwent statistical analysis for other procedure- or patient-related risk factors for PEP performed at single center and by one endoscopist.

PATIENTS AND METHODS

Patients

From January 2012 to December 2016, 1489 patients with native papillae underwent ERCP by a highly experienced endoscopist (D.H.P.) at Asan Medical Center. We excluded 612 patients because of the following criteria: 1) patients who already had acute pancreatitis or acute exacerbation of chronic pancreatitis at procedure time, 2) patients who received precut papillotomy as a transpapillary approach method during ERCP, 3) patients who received pancreatic interventions during ERCP (e.g., pancreatic duct stent and pancreatic fine needle aspiration), 4) patients who received endoscopic ampullary mucosal resection during ERCP, and 5) patients with insufficient clinical data, and 877 patients were enrolled finally. All data were collected retrospectively from the electrical medical records and picture archiving and communication system image. This study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2017-0946).

ERCP procedure

ERCP procedures were performed using a side-view endoscope (Olympus) and involved standard wire-guided pancreatobiliary cannulation. For transpapillary approach methods, endoscopic sphincterotomy (EST) by pull-type papillotome, endoscopic papillary balloon dilatation (EPBD), EST and EPBD, or neither method was used. Bile duct or pancreatic duct cannulation was defined as the passing of the cannulation guidewire or catheter through the bile duct or pancreatic duct, and cannulation number was recorded. All other additive interventions (e.g., transpapillary endobiliary biopsy, nasobiliary drainage insertion, or biliary stent insertion) during ERCP were also recorded. ERCP was performed by a single highly experienced endoscopist (D.H.P.), who has performed >10,000 ERCPs with an average of 500 cases per year.

Definition of PEP

PEP was defined as new-onset abdominal pain persisting for at least 24 h after the procedure and associated with a high serum amylase level equivalent to ≥ 3 times the upper limit of

normal at 12 - 24 h after the procedure. ⁽¹⁴⁾ PEP was graded according to a lexicon for endoscopic adverse events: ⁽¹⁵⁾ mild, requiring fasting and treatment for ≤ 3 days; moderate, requiring fasting and treatment for 4 - 10 days; severe, requiring fasting and treatment for ≥ 10 days, intensive care, or surgical intervention.

Statistical analysis

Statistical analysis included both univariable and multivariable analyses of PEP risk factors by logistic regression. Multivariable model was selected by backward elimination method including variables with a *P* values of < 0.1 in the univariable analysis to identify the independent risk factors for PEP. An adjusted odds ratio (OR) with a 95% confidence interval (CI) that did not include unity was considered significant. All differences were considered significant at a two-sided *P* value of < 0.05 . Data were analyzed using SPSS software (Version 21.0, IBM® SPSS® Statistics).

RESULTS

Patients

In a total 1489 patients, 877 patients were enrolled finally after exclusion criteria. PEP occurred in 34 patients (3.9%) and was mild in 21 patients (2.4%), moderate in 12 (1.4%), and severe in one (0.1%) (Figure 1.). The one severe case was a 44-year-old female who had breast cancer with multiple distant metastases with pancreatic involvement, causing a distal common bile duct obstruction. She had undergone ERCP with a metal biliary stent insertion and had developed PEP the next day. She was managed conservatively and discharged after 17 days. No PEP-related mortality occurred.

Patient characteristics of the 877 patients are shown in Table 1. Mean age was 61.4 years, and 36.6% of the patients were female. Total bilirubin less than 2 mg/dL was observed in 52.4% of patients. When looking at the indications for ERCP, pancreato-biliary stone or sludge was most common (47.8%), followed by pancreatobiliary malignancy (37.4%), benign biliary stricture (6.4%), operation- or procedure-related biliary injury (4.1%), and suspicion of sphincter of Oddi dysfunction (SOD) (0.3%). In table 2, interventions performed during the ERCP procedure are listed and included: EST (N = 691), EPBD (N = 112) or both (N = 44). Biliary stent insertion was performed in 129 patients using a plastic (55 patients) or metal (74 patients) stent.

Patient-related risk factors

Patient-related risk factors for PEP were analyzed using univariable analysis and are shown in Table 1. In PEP group, the patient's age was younger than non-PEP group and showed the statistical significance (PEP group: 56.1 ± 5.5 , non-PEP group: 61.6 ± 1.0) ($P = 0.027$). This supported younger age as the known risk factor for PEP. However, other known risk factors, such as female, total bilirubin less than 2 mg/dL, no biliary stones or suspicion of SOD exhibited no correlation with increased PEP incidence. As for the indications of ERCP, patients with pancreatobiliary stones/sludge showed a lower PEP incidence [10 patients (2.4%); $P = 0.035$]. By dividing the pancreatobiliary malignancy group according to the locations of stricture, patients within the malignant common bile duct (CBD) or ampulla of Vater (AoV)

stricture group showed more frequent PEP occurrence than the overall sample [13 patients (9.4%); $P = 0.001$]. No patient in the malignant intrahepatic duct (IHD) stricture group exhibited PEP, but didn't show the statistical significance ($P = 0.090$).

Procedure-related risk factors

Procedure-related risk factors for PEP identified during univariable analysis are listed in Table 2. In patients in whom transpapillary approach methods were used, no difference was observed in PEP occurrence among no intervention, EST, EPBD or both interventions. Patients in the PEP group exhibited greater pancreatic duct cannulations number (mean = 1.21 ± 0.55) than those in the non-PEP group (mean = 0.42 ± 0.07) ($P < 0.001$). As focusing on the number of pancreatic duct cannulations, PEP occurred in 4.0% of patients who underwent cannulation once, and was not significantly different than that observed in patients who did not undergo cannulation ($P = 0.451$). However, if the cannulation number was two or more, PEP incidence rate significantly increased than no cannulation group. PEP occurred in 8.0% of patients who underwent two cannulations ($P = 0.045$, compared with no cannulation group) and in 14.3% of patients who underwent three or more cannulations ($P < 0.001$, compared with no cannulation group) experienced PEP. However, no difference was observed in bile duct cannulation number between the PEP (mean = 1.35 ± 0.33) and non-PEP (mean = 1.21 ± 0.04) groups ($P = 0.261$).

For the additive biliary interventions, nasobiliary drainage insertion and transpapillary endobiliary biopsy did not related to PEP occurrence. However, in biliary stent insertions, patients who received metal stents showed more frequent PEP than the overall patient group [13 patients (17.6%); mild in 10 patients, moderate in 2 patients, and severe in one patient; $P < 0.001$]. When analyzing the type of metal stent, PEP occurred more with covered metal stents [12 patients (21.1%)] than with uncovered metal stents [one patient (5.9%)]; however, this difference was not statistically significant ($P = 0.179$).

Univariable and multivariable analysis

The results of univariable and multivariable analyses of patient- and procedure-related risk factors for PEP are shown in Table 4. Two or more episodes of pancreatic duct cannulation

remained in the final model. PEP incidence was 3.743 times higher in patients who underwent two cannulations than in those who did not undergo cannulation (Adjusted OR, 3.743; 95% CI, 1.160 - 12.077; $P = 0.027$), and was 5.750 times higher in patients who underwent for three or more cannulations than in those who did not undergo cannulation (Adjusted OR, 5.750; 95% CI, 2.258 - 14.645; $P < 0.001$), indicating a significant difference. These findings are shown in figure 3. Another risk factor, the use of metal biliary stents, also remained in the final model (Adjusted OR, 7.793; 95% CI, 3.614 – 16.803; $P < 0.001$, Table 4). During univariable analysis, other risk factors with P values of < 0.1 (younger age, pancreatobiliary stones/sludge, malignant IHD stricture, or malignant CBD or AoV stricture) were not statistically significant after correcting for other confounding factors.

DISCUSSION

In our study involving 877 patients with native papillae who underwent ERCP procedures, 34 patients (3.9%) had PEP, an incidence rate similar to that observed in previous studies (3% - 6%). All patients exhibited mild (2.4%) or moderate (1.4%) PEP, and most of them improved after several days of conservative management. During multivariable analysis, two risk factors were independent risk factors for PEP, i.e., two or more episodes of pancreatic duct cannulation and use of metal biliary stents.

Two or more episodes of pancreatic duct cannulation was a risk factor for PEP in our analysis. Our center performs standard-of-care cannulation using the guidewire method; therefore, all pancreatic duct cannulations were performed by the guidewire cannulation method. PEP resulting from pancreatic duct cannulation is believed to be caused by mechanical injury of the pancreatic duct.⁽¹²⁾ Passage through the AoV can cause papillary edema, and sphincter hypertension. These conditions may impair pancreatic drainage,⁽¹⁰⁾ as can difficult biliary cannulation.⁽¹⁶⁾ This is thought to be different from the mechanism of pancreatic duct opacification, a hydrostatic and chemical injury.⁽¹⁶⁾ In previous studies, pancreatic duct cannulation was an independent risk factor for PEP,^(5, 10, 12, 13) but these studies did not count the number of cannulations or determine the cut-off value for increased PEP risk. To evaluate PEP risk based on the effects of repeat cannulations and cut-off cannulation number values, we recorded the cannulation number and PEP incidence in each patient. As a control group, PEP occurred in 2.7% of patients who did not undergo cannulation. PEP occurred in 4.0% of patients who underwent only a single cannulation. This incidence was not significantly different from that of the no cannulation group. However, in patients who underwent two or more cannulations, the PEP incidence was significantly greater than that in the no cannulation group; 8.0% of patients with two cannulations experienced PEP, and 14.3% of patients with three or more cannulations experienced PEP. These differences were statistically significant during multivariable analysis. This is important in practice so that clinicians can predict the PEP risk based on the pancreatic duct cannulation number. When the pancreatic duct cannulation number was 0 or 1, the incidence rate of PEP was $\leq 4.0\%$. We consider this rate to be acceptable because it is similar to the overall incidence rate of PEP in our study (3.9%) and in other large

prospective studies (3% - 6%).⁽³⁻⁶⁾ However, PEP incidences in patients who underwent two or more cannulations were higher than the incidence within the overall population, and in such cases preventive measures should be considered. These measures may include pancreatic duct stent placement⁽¹⁷⁾ or medications, such as rectally administered nonsteroidal anti-inflammatory drugs.⁽¹⁸⁻²⁰⁾ The endoscopist can stop the procedure or change to an alternative method, such as precut papillotomy, when an unintended pancreatic duct cannulation occurs or is repeated, although it is controversial as to whether precut papillotomy can reduce the PEP risk.^(16, 21, 22)

By contrast, bile duct cannulation number did not influence the PEP risk, as revealed in univariable and multivariable analyses. In many previous studies, multiple cannulation attempts or difficult cannulation were independent risk factors for PEP,^(3, 8, 9) but our study showed no correlation between the bile duct cannulation number and PEP incidence. This was thought to be because the bile duct cannulation number was mostly low; 825 of 877 patients had undergone fewer than three bile duct cannulations. Only 13 patients had undergone more than six transpapillary cannulations (the sum of bile duct and pancreatic duct cannulation), indicating that, in general, their cannulations were moderately difficult.⁽³⁾ Thirteen patients may be an insufficient sample size for detecting statistical significance. Proving potential relationships between the bile duct cannulation number and PEP incidence will require additional large-scale studies.

Another procedure-related factor, the use of metal biliary stents emerged as a risk factor for PEP in our study. Compared with the plastic biliary stent insertion group (0%), the PEP incidence rate was high (17.6%) in the metal biliary stent insertion group and showed statistical significance in multivariable analysis. There is a controversy regarding the biliary stent insertion as a risk factor for PEP, but some recent studies have concluded that the biliary stent insertion is a risk factor for PEP. These studies identified both plastic and metal stents⁽²³⁾ or metal stents only.⁽²⁴⁾ It is possible that the biliary stent insertion distorts the CBD and compresses the pancreatic duct or common channel, forming a pancreatic duct orifice obstruction.⁽²⁴⁾ Symptoms associated with metal biliary stent insertion may appear more severe because these stents feature a larger diameter than plastic biliary stents. PEP incidence was higher in patients with covered metal biliary stents than in those with uncovered metal

biliary stents (21.1% vs 5.9%); however, this difference was not statistically significant ($P = 0.173$). This trend was similar to those observed in previous studies. ^(25, 26) To find the relationship between the covered metal biliary stent and PEP incidence rate, further larger-scale studies are needed.

Our study has some limitations. First, the study design was retrospective and involved a single center, with procedures performed by a single endoscopist. This could bias the clinical data, and different results could be observed if data were obtained from other groups. However, a single center with procedures performed by a single highly experienced endoscopist could have an advantage in correcting for center volume- or expert procedure-related factors. Nevertheless, additional prospective randomized clinical trials are needed. Second, patients who underwent precut papillotomy or pancreatic duct stents were excluded from this study. Although we excluded these patients as those factors could affect the PEP incidence, comparing them with the overall group might also be helpful for revealing a potential relationship with PEP incidence. Third, very few patients underwent pancreatic duct cannulation more than four times or bile duct cannulation more than six times. This limited our ability to analyze the association between the cannulation number and the proportionally increasing PEP incidence rates. This was because rather than continuing the cannulation, our center tends to stop or switch the procedure to precut papillotomy or endoscopic ultrasonography-guided drainage if the cannulation is perceived to be difficult. Further large-scale studies are needed to discern potential relationships between the cannulation number and PEP incidence rate. Lastly, the number of patients with SOD was extremely small. SOD is well known risk factor for PEP. ^(2, 5, 16, 21, 27) However, our center does not use the sphincter of Oddi manometry to routinely diagnose SOD; therefore, a correct diagnosis of SOD might have been absent and the number of patients diagnosed with SOD might have been underestimated and did not show the relationship between the SOD and PEP incidence rate.

CONCLUSION

In conclusion, pancreatic duct cannulation and metal biliary stent insertion were associated with increased PEP incidence in patients undergoing ERCP performed by highly experienced endoscopist. As for the pancreatic duct cannulation, two or more cannulations considerably increased PEP incidence. This suggested that preventive measures, such as pancreatic duct stent placement or rectally administered nonsteroidal anti-inflammatory drugs or alternative cannulation measures might be considered in patients with two or more cannulations or those undergoing metal biliary stent insertion.

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국문요약

배경 및 목적: 내시경역행담췌관조영술 (Endoscopic retrograde cholangiopancreatography, ERCP) 후 발생하는 췌장염 (Post-ERCP pancreatitis, PEP)은 ERCP의 주요 합병증 중 하나이며, 심할 경우 사망에 이를 수도 있다. 췌관 삽관을 비롯하여 여러 가지 PEP와 관련된 위험인자가 밝혀져 있으나 췌관 삽관의 횟수와 PEP의 위험도와의 관계는 지금까지 연구된 바가 없다. 본 연구에서는 PEP 발생에 있어 반복적인 췌관 삽관과의 연관성 및 그 외의 다른 위험인자들을 밝히고자 한다.

방법: 2012년 1월부터 2016년 12월까지 울산대학교 서울아산병원에서 ERCP 시술을 받은 환자 중 이전에 유두를 통한 삽관을 받은 적이 없는 877명을 대상으로 후향적 분석을 시행했다. PEP 발생률과 환자 및 시술과 관련된 위험인자들의 관련성 확인하기 위해 단변량 및 다변량 로지스틱 회귀분석을 시행했다.

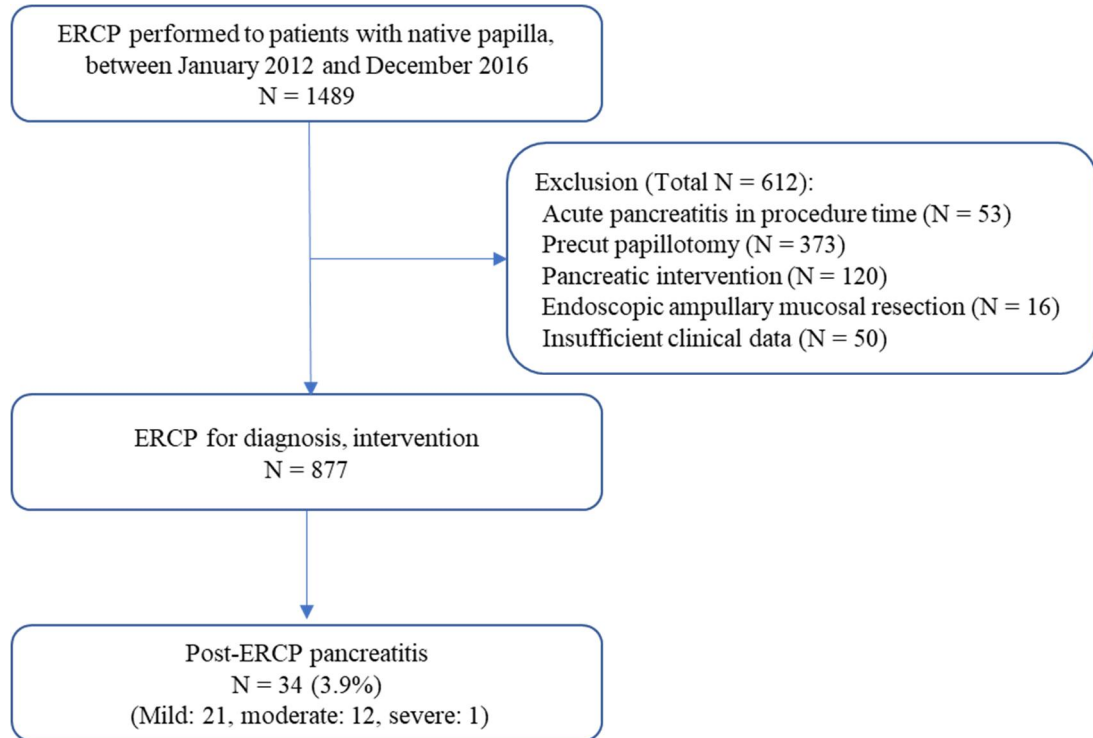
결과: ERCP의 적응증으로는 췌담도석 또는 췌담도 슬러지가 47.8%로 가장 많았으며 췌담도계의 악성질환이 37.4%로 그 다음을 차지했다. PEP는 총 3.9%에 해당하는 34명의 환자에게 발생했고, 21명이 경증, 12명이 중등증, 그리고 1명의 중증이였다. 단변량 분석을 시행한 결과 낮은 연령, 악성 총담관 또는 바터 팽대부 폐색, 2회 이상의 췌관 삽관, 금속 담관 스텐트 삽입이 PEP 발생의 위험인자로 확인됐으며, 췌담도석 또는 췌담도 슬러지는 PEP 발생의 보호인자로 확인됐다. 이후 시행한 다변량 분석에서는 2회 이상의 췌관 삽관과 금속 담관 스텐트 삽입이 PEP 발생의 독립적인 위험인자로 최종적으로 확인됐다. 췌관 삽관의 경우 1회까지는 PEP 발생률이 4.0% 정도로 의미 있는 차이를 보이지 않았으나 2회에서는 8.0%, 3회 이상에서는 14.3%로 발생률이 의미 있게 증가했다.

결론: 본 연구를 통해서 숙련된 내시경 의사에게 ERCP를 시행 받은 환자들에게서 췌관 삽관 및 금속 담관 스텐트 삽입이 PEP 발생의 위험인자로 확인됐다. 췌관 삽관의 경우 2회 이상 시행될 경우 PEP 발생률이 의미 있게 증가했다. 따라서 2회 이상의 췌관 삽관이나 금속 담관 스텐트 삽입이 이루어진 환자에게는 예방적으로 췌관 스텐트를 삽입하거나 직장 내 비스테로이드소염제 투약을 고려해 볼 수 있겠다.

중심단어: 내시경역행담췌관조영술, ERCP 후 췌장염, 췌관 삽관, 금속 담관 스텐트.

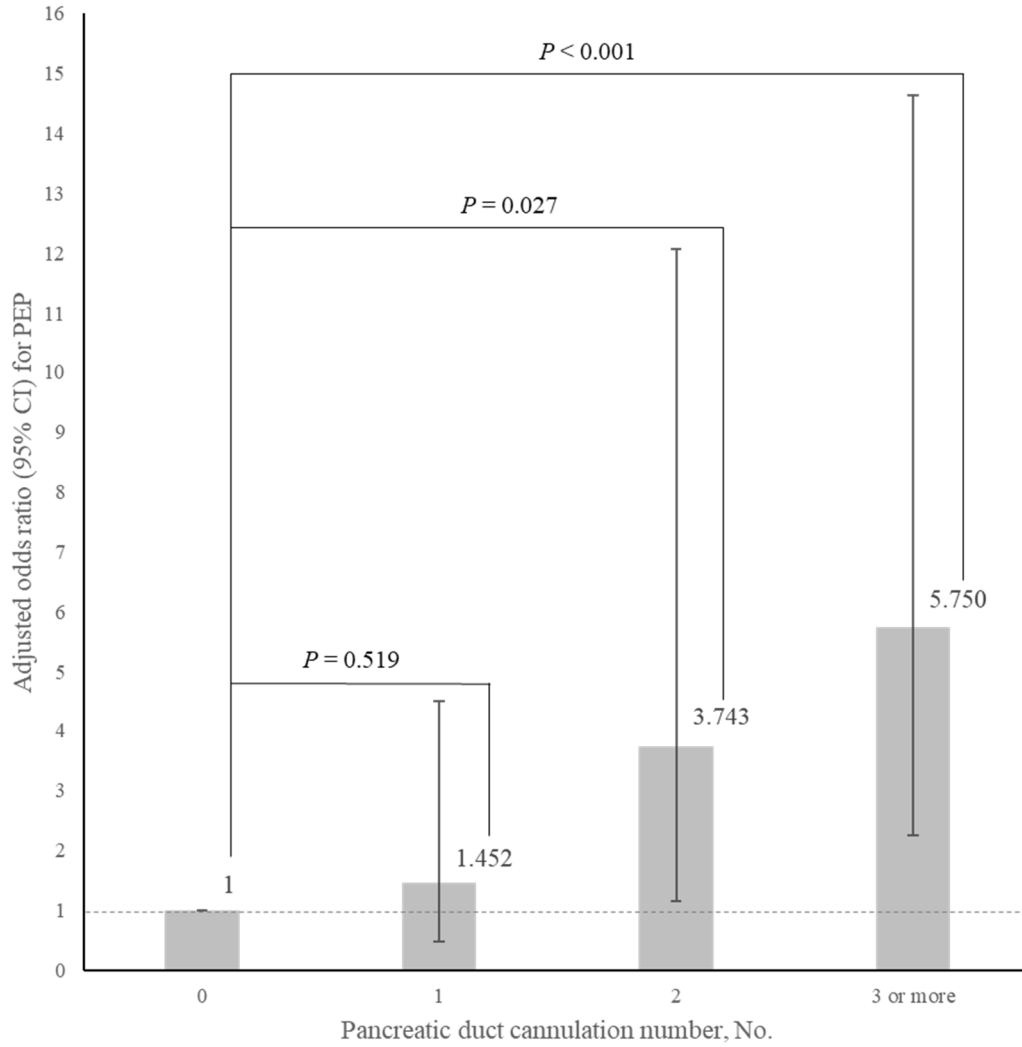
Figures

Figure 1. Flowchart of patients included in the study



ERCP, endoscopic retrograde cholangiopancreatogram.

Figure 2. Pancreatic duct cannulation number and odds ratio for PEP, by multivariable analysis



PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis

Tables

Table 1. Patient-related risk factors and incidence of PEP

Variables	Total (N = 877)	PEP (N = 34)	Non-PEP (N = 843)	P value
Age, mean, years	61.4 ± 1.0	56.1 ± 5.5	61.6 ± 1.0	0.027
BMI, mean, kg/m ²	23.4 ± 0.2	23.2 ± 1.0	23.4 ± 0.2	0.723
Female, No. (%)	321 (36.6)	11 (3.4)	310 (96.6)	0.600
Alcohol drinker, No.	869			
Non-drinker, No. (%)	445 (51.2)	20 (4.5)	425 (95.5)	Reference
Past drinker, No. (%)	108 (12.4)	1 (0.9)	117 (99.2)	0.117
Current drinker, No. (%)	316 (36.4)	13 (4.2)	293 (95.8)	0.800
Smoker, No.	873			
Non-smoker, No. (%)	509 (58.3)	21 (4.1)	488 (95.9)	Reference
Past smoker, No. (%)	223 (25.5)	6 (2.7)	217 (97.3)	0.347
Current smoker, No. (%)	141 (16.2)	7 (5.0)	134 (95.0)	0.665
Total bilirubin < 2mg/dL, No. (%)	447/853 (52.4)	12 (2.7)	435 (97.3)	0.125
Biliary stone, No. (%)	262 (29.9)	7 (2.7)	255 (97.3)	0.232
Indications of ERCP, No. (%)				
Pancreatobiliary stones/sludge, No. (%)	417 (47.8)	10 (2.4)	407 (97.6)	0.035
Benign biliary stricture, No. (%)	56 (6.4)	4 (7.1)	52 (92.9)	0.200
Pancreatobiliary malignancy, by locations of stricture	328 (37.4)			
IHD stricture, No. (%)	66 (7.5)	0 (0)	66 (100)	0.090
Hilar stricture, No. (%)	119 (13.6)	3 (2.5)	116 (97.5)	0.410
CBD or AoV stricture, No. (%)	139 (15.8)	13 (9.4)	126 (90.6)	0.001
Other malignancy, No. (%)	4 (0.5)			
Operation or procedure related biliary injury, No. (%)	36 (4.1)	3 (8.3)	33 (91.7)	0.157
Suspicion of SOD, No. (%)	3 (0.3)	0 (0)	3 (100)	0.728

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

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; IHD, intrahepatic duct; CBD, common bile duct; AoV, ampulla of Vater; SOD, sphincter of Oddi dysfunction.

Table 2. Procedure-related risk factors and incidence of PEP

Variables	Total (N = 877)	PEP (N = 34)	Non-PEP (N = 843)	P value
Transpapillary approach methods				
No interventions, No. (%)	30 (3.4)	1 (3.3)	29 (96.7)	Reference
EST, No. (%)	691 (78.8)	26 (3.8)	665 (96.2)	0.904
EPBD, No. (%)	112 (12.8)	6 (5.4)	106 (94.6)	0.652
EST + EPBD, No. (%)	44 (5.0)	1 (2.3)	43 (97.7)	0.784
Cannulation attempts				
Total cannulation number, mean	1.67 ± 0.08	2.56 ± 0.55	1.64 ± 0.08	
Bile duct cannulation number, mean	1.22 ± 0.5	1.35 ± 0.33	1.21 ± 0.04	0.261
Pancreatic duct cannulation number, mean	0.45 ± 0.07	1.21 ± 0.55	0.42 ± 0.07	<0.001
Cannulation number				
0	672 (76.6)	18 (2.7)	654 (97.3)	Reference
1	99 (11.3)	4 (4.0)	95 (96.0)	0.451
2	50 (5.7)	4 (8.0)	46 (92.0)	0.045
3 or more	56 (6.4)	8 (14.3)	48 (85.7)	<0.001
Additive interventions				
Plastic biliary stent insertion, No. (%)	55 (6.3)	0 (0)	55 (100)	0.124
Metal biliary stent insertion, No. (%)	74 (8.4)	13 (17.6)	61 (82.4)	<0.001
Uncovered metal stent, No. (%)	17 (1.9)	1 (5.9)	16 (94.1)	Reference
Covered metal stent, No. (%)	57 (6.5)	12 (21.1)	45 (78.9)	0.179
Nasobiliary drainage insertion, No. (%)	442 (50.4)	14 (3.2)	428 (96.8)	0.275
Transpapillary endobiliary biopsy, No. (%)	159 (18.1)	5 (3.1)	154 (96.9)	0.598

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

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilatation.

Table 3. Univariable and multivariable logistic regression analyses of risk factors of PEP

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	<i>P</i> value	Adjusted odds ratio (95% CI)	<i>P</i> value
Patient-related factors				
Age	0.975 (0.953-0.997)	0.027	0.978 (0.954-1.002)	0.070
Indications of ERCP				
Pancreatobiliary stones/sludge	0.446 (0.211–0.945)	0.035	0.673 (0.267-1.695)	0.400
Pancreatobiliary malignancy, by locations of stricture				
IHD stricture	0.958 (0.944-0.972)	0.090	0	0.997
CBD or AoV stricture	3.523 (1.720–7.216)	0.001	1.223 (0.466–3.213)	0.683
Procedure-related factors				
Pancreatic duct cannulation number				
0	Reference			
1	1.530 (0.507-4.617)	0.451	1.452 (0.467-4.513)	0.519
2	3.159 (1.027-9.721)	0.045	3.743 (1.160-12.077)	0.027
3 or more	6.056 (2.504-14.642)	<0.001	5.750 (2.258-14.645)	<0.001
Additive interventions				
Metal biliary stent insertion	7.936 (3.790-16.619)	<0.001	7.793 (3.614-16.803)	<0.001

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; IHD, intrahepatic duct; CBD, common bile duct; AoV, ampulla of Vater.