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Original Article

Post-ERCP pancreatitis and its related factors: A prospective study in Cipto Mangunkusumo National General Hospital

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Abstract

Objectives: Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used procedure for the diagnosis and treatment of pancreatobiliary disease with post-ERCP pancreatitis (PEP) is the most common complication. The goal of this study was to comprehensively evaluate the potential patient- and procedure-related risk factors for PEP. **Methods:** A 25-variable database was compiled from information collected before, during, and 24–72 h after ERCP for 238 patients who underwent diagnostic or therapeutic ERCP in Cipto Mangunkusumo General National Hospital, Jakarta. The grading of acute pancreatitis was classified using the modified Glasgow (Imrie's) severity criteria. **Results:** The average age was 51 years, and most patients were men and were overweight. Sixty-three patients (26.5%) were diagnosed with PEP, and 33 of these (52.4%) were classified as having severe pancreatitis. We applied univariate analysis to analyze the data contained in the 25-variable database to identify patient- and procedure-related predictors of PEP. We found significant correlations between PEP and the patient-related factor common bile duct stenosis ($P < 0.05$), and between PEP and the three procedure-related factors procedure time, cannulation time, and multiple cannulation attempts ($P < 0.05$). Multivariate analysis showed that multiple attempts at cannulations was the only significant risk factor for PEP. **Conclusions:** In our study, four variables were associated with PEP: Common bile duct stenosis, procedure time, cannulation time, and multiple attempts at cannulations. We conclude that, in patients undergoing ERCP who are at high risk of PEP, procedure-related factors should be monitored to reduce the risk of PEP. Multiple attempts at cannulation was the most significant risk factor in our study.

Key words Endoscopic retrograde cholangiopancreatography, pancreatitis, postendoscopic retrograde cholangiopancreatography pancreatitis, risk factors

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has become a commonly performed endoscopic procedure for diagnostic and therapy in a variety of gastrointestinal disorders, including biliary duct stones and pancreatobiliary neoplasms. Despite the recent advances in medical technology and experience of endoscopists, the use of ERCP may still leads to serious complications such as bleeding, perforation, and acute pancreatitis.

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Pancreatitis remains the most common severe complication of ERCP.[1,2] A review by Lazaraki and Katsinelos reported that post-ERCP pancreatitis (PEP) is the most common complication of ERCP and that its frequency is 2.1–39%. This varying incidence is thought to relate to many factors.[3]

PEP is defined as an acute pancreatitis that has developed following ERCP. A widely used consensus definition for PEP is (1) new or worsened abdominal pain, (2) new or prolonged hospitalization for at least 2 days, and (3) serum amylase concentration ≥3 times the upper limit of the normal range, measured >24 h after the procedure.[4]

In Indonesia, there is no established prospective study of PEP and its related factors. This prompted us to conduct a prospective and cross-sectional study to evaluate the potential patient- and procedure-related risk factors for PEP in Cipto Mangunkusumo National General Hospital, Jakarta.

Methods

This study was a prospective, cross-sectional study. Ethical clearance was given by the Ethical Committee of the Faculty of Medicine, Universitas Indonesia (registered ethical approval number 616/PT02.FK/ETIK/2012). The subjects were patients who underwent ERCP for the 1st time and were recorded as patients in Cipto Mangunkusumo National General Hospital.

In total, 266 ERCPs were performed during the period June 2013 to May 2014. All subjects completed and signed an informed consent form. Patients who had acute pancreatitis at the time of presentation for ERCP were excluded. Patients who had past history of pancreatitis were not excluded. The diagnosis of acute pancreatitis was made on the basis of two of the following three criteria: (1) Abdominal pain, (2) serum amylase ≥3 times the upper limit of the normal range, and (3) significant findings on radiology indicating acute pancreatitis.[5]

Data about the patients' demography; gastrointestinal symptoms such as persistent abdominal pain or radiating pain to the back, nausea, and vomiting; vital signs; laboratory findings; and ERCP procedure details such as the procedure time, cannulation time, number of cannulations, balloon dilation, stenting, brushing biopsy, and sphincterotomy, were collected prospectively before, during, and 24–72 h after the procedure.

Acute pancreatitis was graded according to the modified Glasgow (Imrie's) severity criteria. The criteria are age >55 years, arterial oxygen tension <8 kPa, white cell count >15 × 10^9, serum calcium concentration <2 mmol/L, serum urea concentration >16 mmol/L, lactate dehydrogenase concentration >600 IU/L or aspartate transaminase/alanine transaminase concentration >200 IU/L, serum albumin concentration <32 g/L, and blood glucose concentration >10 mmol/L. The presence of ≥3 of these criteria within the first 48 h was considered indicative of severe pancreatitis.[6]

All data were entered into a 25-variable database. The statistical analysis was performed using SPSS software (version 21.0; IBM SPSS, Armonk, NY, USA). Correlations between all risk factors and PEP incidence were analyzed using the Chi-square test and independent *t*-test. For all tests, $P < 0.05$ was considered significant.

Results

Two hundred and sixty-six patients were eligible to participate in this study for a clinically indicated ERCP at the Cipto Mangunkusumo National General Hospital. The indications for the procedure were mostly obstructive jaundice. Twenty-eight patients were excluded because they had presented with acute pancreatitis before the ERCP. After exclusion of these patients, 238 patients were enrolled in this study. Most of the ERCP procedures were therapeutic ERCP. Among 238 patients who underwent ERCP in this study, 6 of them were diagnostic ERCP. There were also seven cases of pancreatic intervention by placement of pancreatic stent with the indication of precut sphincterotomy due to difficult cannulation. All of the cases were performed by more than one consultant. Part of them were carried out by trainees (with close supervision by consultant). All of the consultants had experience performing ERCP for more than 10 years. The demographic data from each group and the patient-related factors are presented in Table 1.

The average age of the patients was 51 years, ranged from 23 to 85 years. One hundred and thirty-two patients (55.5%) of the subjects were men and 106 (44.5%) were women. Most patients were overweight with mean body mass index (BMI) of 23.6 kg/m^2, ranged from 14.3 to 30.3 kg/m^2. Additional data regarding BMI are presented in Table 1. Table 1 also shows the data for laboratory findings, the origin of pancreatobiliary disease included a tumor of the ampulla of Vater, common bile duct stenosis, common bile duct stones, and tumor of the head of the pancreas. We separated the patients into two groups according to the presence and absence of PEP. Sixty-three patients had PEP (26.5%), and 33 of these patients (52.4%) had severe pancreatitis. We found no significant correlations between patient-related factors and the presence of PEP.

The procedure-related factors are shown in Table 2. The definition of procedure time was the time required for completion of the intended procedure. The definition of cannulation time was the time required from contact of ampulla to deep cannulation. We used accessory for cannulation including ERCP cannula and sphincterotome. The technique used for cannulation was wire guided technique. The definition of cannulation attempts was the number of

Table 1: Patient-related factors

Factor	Total (*n*=238)	PEP (*n*, %)		*P*	OR	95% CI
		Yes (*n*=63)	No (*n*=175)			
Age,<60 years	51.0 (SD: 12.8)	51.3 (13.6)	50.8 (12.6)	0.732*	0.88	0.45-1.75
Gender, *n* (%)						
Male	132 (55.5)	34 (54)	98 (56)	0.781*	0.92	0.52-1.64
Female	106 (44.5)	29 (46)	77 (44)	0.392**	0.58	0.16-2.07
BMI†, kg/m^2	23.6 (SD: 3.2)	23.1 (3.2)	23.8 (3.2)			
Hemoglobin, g/dL	11.31 (SD: 1.83)	11.4 (1.7)	11.3 (1.9)	0.288*	1.47	0.72-3.00
White blood cell count, cells/μL	9958 (SD: 4643)	9732 (4498)	10,037 (4703)	0.815*	1.08	0.59-1.96
Bilirubin, mg/dL	10.6 (SD: 10.3)	13.7 (12.5)	9.5 (9.25)	0.053*	0.47	0.22-1.02
Albumin, g/dL	3.23 (SD: 0.75)	3.24 (0.64)	3.23 (0.78)	0.283*	1.40	0.76-2.60
Urea, mg/dL	30 (SD: 24.77)	26.75 (22.61)	31.1 (25.4)	0.257*	1.65	0.69-3.98
Creatinine, mg/dL	1.06 (SD: 1.6)	0.83 (0.44)	1.15 (1.8)	0.839*	1.09	0.46-2.57
RBG‡, mg/dL	112 (SD: 33.8)	114.8 (39.7)	111.2 (31.5)	0.186*	0.57	0.25-1.60
Amylase, U/L	84 (SD: 271)	66 (87)	90.1 (310.63)	0.879*	0.95	0.51-1.78
Lipase, U/L	124 (SD: 447)	100 (149.8)	131.8 (512.3)	0.619*	0.86	0.47-1.55
Diabetes mellitus, *n* (%)	36 (SD: 15.1)	12 (19)	24 (13.7)	0.311*	0.67	0.31-1.44
Tumor of the ampulla of Vater, *n* (%)	30 (12.6)	7 (11.1)	23 (13.1)			
Common bile duct stenosis, *n* (%)	74 (31.1)	34 (47.6)	40 (22.8)	0.677*	0.83	0.34-2.03
Common bile duct stones, *n* (%)	78 (32.8)	17 (27)	61 (35)	0.042*	0.54	0.30-0.98
Tumor of the head of the pancreas, *n* (%)	26 (10.9)	5 (7.9)	21 (12)	0.254*	0.69	0.36-1.30
Normal ERCP/other causes, *n* (%)***	30 (12.6)	0 (0)	30 (14.8)	0.375*	0.63	0.23-1.75

*Chi-square test, **Independent *t*-test, †BMI=Body mass index, ‡RBG=Random blood glucose, ***Only 6 patients showed normal ERCP and all patients in this study didn't have any sign of pancreatitis before ERCP. Other causes in this table is all patients who underwent ERCP out of four main causes (tumor of the ampulla of Vater, common bile duct stenosis, common bile duct stones, tumor of the head of the pancreas) and maybe caused by inflammation of the bile duct or other unexplainable causes. PEP=Post-ERCP pancreatitis, ERCP=Endoscopic retrograde cholangiopancreatography, SD=Standard deviation, OR=Odds ratio, CI=Confidence interval

Table 2: Procedure-related factors

Factor	Total (*n*=238)	PEP (%)		*P**	OR	95% CI
		Yes (*n*=63)	No (*n*=175)			
Procedure time (min), *n* (%)						
≤50	83 (34.9)	11 (17.5)	72 (41.1)	0.001	0.30	0.14-062
>50	155 (65.1)	52 (82.5)	103 (58.9)			
Cannulation time (min), *n* (%)						
≤25	143 (60.1)	31 (49.2)	112 (64)	0.040	0.54	0.30-0.97
>25	95 (39.9)	32 (50.8)	63 (36)			
Number of cannulations, *n* (%)						
≤2	171 (71.8)	25 (39.7)	146 (83.4)	0.001	1.31	0.07-0.25
>2	67 (28.2)	38 (60.3)	29 (16.6)			
Balloon dilation, *n* (%)						
Yes	90 (37.8)	22 (34.9)	68 (38.9)	0.581	0.84	0.46-1.53
No	148 (62.2)	41 (65.1)	107 (61.1)			
Stenting, *n* (%)						
Yes	123 (51.7)	36 (57.1)	87 (49.7)	0.312	1.35	0.75-2.41
No	115 (48.3)	27 (42.9)	88 (50.3)			
Brushing/biopsy, *n* (%)						
Yes	49 (20.6)	13 (20.6)	36 (20.6)	0.991	1.00	0.49-2.05
No	189 (79.4)	50 (79.4)	139 (79.4)			
Endoscopic sphincterotomy, *n* (%)						
Yes	155 (65.1)	35 (55.6)	120 (68.6)	0.063	0.57	0.32-1.03
No	83 (34.9)	28 (44.4)	55 (31.4)			

*Chi-square test. PEP=Post-ERCP pancreatitis, ERCP=Endoscopic retrograde cholangiopancreatography, OR=Odds ratio, CI=Confidence interval

cannulation performed until deep cannulation was succeed. Selective deep cannulation was achieved in all cases. Stent placements were done with and without sphincterotomy. Among 238 patients who underwent ERCP in this study, 123 patients were underwent biliary stent placement. Among all patients with biliary stent placement, 81 patients were without sphincterotomy. The number of cases in which the contrast was injected to pancreatic duct were only 3 and the number of cases in which the accessory (guidewire) was entered into the main pancreatic duct were only 8. Sphincterotomy performed in this study were endoscopic sphincterotomy. There was a significant correlation between the procedure time, cannulation

time, and number of attempted cannulations during the ERCP procedure and an increased risk of PEP.

Multivariate analysis was performed using logistic regression test. Only the number of attempted cannulations was associated with an increased risk of PEP. As our hospital is a gastrointestinal endoscopy training center in Indonesia, some ERCP procedures were carried out by trainees with close supervision by consultants.

Discussion

The primary aim of this study was to identify the risk factors for PEP. We evaluated whether patient- and procedure-related factors were related to the risk of PEP. The results of this study differ from those in some previous studies that reported that age, gender, obesity, and procedure-related risk factors such as precut sphincterotomy and pancreatic duct injection significantly increased the risk of PEP. Our study found that only the procedure time, cannulation time, and multiple cannulations were associated with an increased risk of PEP.

In our study, 77.7% of the patients were aged <60 years, and we found no significant correlation between age and PEP. In some multicenter studies, age <60 years was related to a high risk of PEP.[7-9] However, Cotton *et al*., found no correlation between age and PEP.[10] In their review article, Feurer and Adler concluded that younger age, specifically in patients aged <60 years, is associated with an increased risk of PEP.[11,12] Lukens *et al*., reported that the PEP complications rate was significantly higher in patients aged <80 years (110 patients, 3.45%) than in those aged >80 years (12 patients, 1.65%).[13]

In our study, female gender was not associated with the risk of PEP. This observation is consistent with that of another study by Cheng *et al*. which reported that female gender, history of recurrent idiopathic pancreatitis, pancreas divisum, sphincter of Oddi manometry, difficult cannulation, and major papilla sphincterotomy (either biliary or pancreatic) were not risk factors for PEP.[7] However, female gender was suggested as a possible risk factor for PEP by Feurer and Adler.[11] Most previous studies have found a higher risk in patients with sphincter of Oddi dysfunction, a condition that occurs primarily in women.[7,14] Suspected sphincter of Oddi dysfunction independently triples the risk of PEP to a frequency of 23%.[14,15] We did not have any patient with sphincter of Oddi dysfunction, which may be a factor affecting the results of the study and/or showing different results from other published studies.

Obesity may be an independent risk factor for severe PEP.[10] However, we found no significant correlation between obesity and PEP. The average BMI data indicated that most of our patients were overweight (144 patients/60.5%) with mean BMI of 23.6 kg/m^2 in both the PEP-positive and PEP-negative groups. Other studies have not identified obesity as an independent risk factor.[16,17]

Some studies have linked laboratory findings in diagnosing acute pancreatitis. The pancreas is the primary source of serum lipase. Serum lipase level increases 4–8 h after ERCP and remains elevated for 8–14 days. Serum amylase level is not related to the cause of pancreatitis.[18] In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.[5] We found no correlations between PEP and amylase/lipase levels.

Leukocytosis and/or fever are signs of severe systemic toxicity in acute pancreatitis. We found no correlation between PEP and leukocytosis, between PEP and anemia, or between PEP and bilirubin level. By contrast, Freeman *et al*. reported that a normal serum bilirubin level increased the risk of PEP.[15]

We also evaluated other laboratory findings such as urea and creatinine, and random blood glucose concentrations. Overall, our results are similar to those reported by Nader *et al*., who found that hemoglobin level, white blood cell count, and blood glucose, urea, creatinine, albumin, and bilirubin levels were not significant risk factors for PEP.[19]

In our study, diabetes mellitus as a comorbid condition was not associated with PEP. This result differs from that reported by Sekimoto *et al*. and Kadayifci. Sekimoto *et al*. reported that secondary hyperlipidemia, which was related to diabetes mellitus, was a risk factor for PEP.[20] In Kadayifci's study, the incidence of pancreatitis was more severe in patients with diabetes mellitus compared with age- and sex-matched patients without diabetes.[21]

All patients who enrolled this study had been registered with various diagnoses in Cipto Mangunkusumo National General Hospital. Many patients were diagnosed with common bile duct stones (32.8%), followed by common bile duct stenosis (31.1%), tumor of the ampulla of Vater (12.6%), and tumor of the head of the pancreas (10.9%). We found that common bile duct stenosis was associated with increased incidence of PEP. In patients with common bile duct stenosis, the ERCP procedure takes longer because of difficulties with cannulation or the need for multiple cannulations. All of the common bile duct stenosis cases in our study were malignant. Our study showed that procedure time and multiple cannulations attempted were risk factors for PEP. These findings strongly suggest that common bile duct stenosis is a risk factor for PEP.

We identified that, of all variables tested, procedure time, cannulation time, and multiple cannulations significantly increase the risk of PEP. Other studies showed a similar result.[22,23] Ozaslan concluded that the main cause of difficulty in cannulation is the anatomical structure of intrapapillary ducts which comprises complex mucosal features and that repetitive trauma to the mucosa can lead to PEP.[24-26] Wang *et al*. also

identified a cannulation time of >10 min as a significant risk factor for PEP.[8] In our study, we use 25 min as the cut-off point for delayed cannulation time because some of the procedures were conducted by trainees. This may also be a factor in the fairly high incidence of PEP and severe pancreatitis.

Large prospective studies have identified several variables as risk factors for PEP. Jeurnink *et al*. found seven patient- and procedure-related risk factors that were significantly associated with PEP: Pancreas divisum, age <60 years, female gender, difficult cannulation, precut sphincterotomy, multiple pancreatic duct contrast injections, and a history of previous PEP.[27] A meta-analysis by Masci *et al*. analyzed 15 prospective clinical studies and identified five patient-and nine procedure-related risk factors for PEP including precut sphincterotomy and pancreatic duct injection.[28]

A proper understanding of the patient- and procedure-related risk factors has led to a strategy for avoiding unnecessary ERCP (especially for diagnostic purpose only) and using alternative modalities such as endoscopic ultrasonography and magnetic resonance cholangiopancreatography. Other alternatives to reduce the risk of PEP, when ERCP is performed include pharmacological interventions, short-term placement of a pancreatic duct stent, and guide wire cannulation, which are effective in reducing the risk of PEP.[29-33] The European Society of Gastrointestinal Endoscopy 2014 guidelines recommend routine rectal administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindications.[34]

For prevention of PEP, it has also been recommended that a small-caliber stent be placed into the pancreatic duct relatively early in the procedure in all high-risk circumstances and in patients whose cannulation might be difficult cannulation such as younger, female patients or those with a normal pancreas.[14] The meta-analysis by Choudhary *et al*., supports this recommendation which found that prophylactic pancreatic stent placement significantly decreased the incidence of PEP.[35] In our center, we sometimes place the pancreatic stent or administer somatostatin to prevent PEP. All patients who underwent somatostatin administration were excluded from this study. All patients (seven patients) who underwent pancreatic placement due to difficult cannulation were included in this study.

Conclusion

This study aim to identify patient- and procedure-related factors associated to the risk of PEP. The incidence of PEP in our study was 26.5%. Our study showed that common bile stenosis was the only patient-related factor associated with PEP. There were three procedure-related factors associated with PEP, including procedure time, cannulation time, and multiple cannulations. Multiple attempts at cannulation was the most significant risk factor of PEP in our study. We conclude that in patients undergoing ERCP who are at high risk of PEP, procedure-related factors should be monitored closely to reduce the risk of PEP.

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Conflicts of interest

There are no conflicts of interest.

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