

Is fatty liver associated with post-ERCP pancreatitis?

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Abstract

Background: Acute pancreatitis remains the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Several factors have been already found associated with post ERCP pancreatitis (PEP), although there is still controversy in some areas. **Aim:** We aim to identify possible risk factors associated with PEP in a referral tertiary center. **Method and Material:** All patients undergoing ERCP from 2013 to 2016 in our university hospital were enrolled and their data including demographic, clinical, paraclinical and endoscopic information were reviewed. Patients meeting the criteria for PEP were identified and the severity of PEP was determined. Data from patients diagnosed with PEP was compared to the rest. Technical/operator variables were unchanged during our study period of 3 years. Incomplete patients' files were omitted. We had no exclusion criteria. **Results:** Of the 462 patients (200 women, 262 men; mean age of 59 with age range: 21-92), PEP developed in 24 patients (5.2%) among who, 19 cases were mild, 4 were moderate and one was severe. Significant variables (both patient- and endoscopic-related) found associated with PEP were fatty liver ($P=0.04$), difficult cannulation ($p=0.001$) and balloon dilatation ($p=0.001$). PEP was not associated with age or gender, history of smoking or alcohol use, and comorbidities (including diabetes mellitus, hypertension, ischemic heart disease, cancer, cirrhosis, inflammatory bowel disease). Regarding the laboratory data, liver enzymes were significantly higher in PEP patients and creatinine level was significantly lower in this group. However, hemoglobin and bilirubin, erythrocyte sedimentation rate (ESR), lipid profile, platelet and WBC count and amylase level before ERCP showed no significant relation with PEP. Using statin was associated with decreased PEP frequency. Among endoscopic-related factor, precut, brush cytology and sphinctrotomy were not related with PEP. Of the total ERCPs, 62% were successful, 25.5% were partially successful and 9.5% failed. According to pathology results, the etiology was CBD stone in 75%, malignancy in 24% and undetermined in the remaining 1%. Neither ERCP result nor final pathologic diagnosis were associated with PEP. **Conclusion:** Patients with fatty liver might be at higher risk for developing PEP. On the other hand, statins might play a role in reducing the incidence of PEP.

Keywords: endoscopic retrograde cholangiopancreatography (ERCP), Post ERCP pancreatitis (PEP).

INTRODUCTION

Acute pancreatitis remains the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Reported prevalence of post procedure pancreatitis ranged from 1.3% to 8% in large prospective studies [1, 2] while occurring in up to 30-40% of high-risk patients [3, 4]. A recent meta-analysis of 108 randomized, controlled trials (RCTs) reported an overall incidence of 9.7%, with a mortality rate of 0.7% [5].

Many studies have investigated risk factors of PEP although there is still controversy in some areas. Moreover, predictors for severity of PEP are not well established, primarily due to limited data. Patient-related characteristics that were statistically significant as risk factors of PEP by multivariate analysis included younger age, female gender, suspected or proven sphincter of Oddi dysfunction, prior post-ERCP pancreatitis, a normal serum bilirubin, and recurrent pancreatitis [6-11]. Several procedure-related factors are known to increase the risk of PEP in multivariate prospective studies or meta-analyses. Most importantly difficult cannulation

(characterized by a greater number of attempts or longer time needed to successfully cannulate the bile duct) can result in trauma to the ampulla leading to increased risk of PEP [1, 6, 9]. Moreover, pancreatic duct cannulation, more than one passage of a pancreatic guide wire, pancreatic duct injection/pancreatogram, precut sphincterotomy, pancreatic

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sphincterotomy, and ampullectomy have also repeatedly been identified as independent risk factors for post-ERCP pancreatitis [6, 10-16]. There are also some controversial risk factors of PEP in studies such as some potentially pancreato-toxic drugs such as valproic acid, azathioprine or estrogen, smoking, and the absence of a common bile duct stone which require further investigations. In addition, there is conflicting evidence regarding the influence of endoscopist's experience, the procedure volume of a specific center, and the involvement of trainees on the risk of post-ERCP pancreatitis [7].

In this study we aim to identify the variables effective on PEP incidence and its severity. Identifying factors associated with PEP are essential to recognize high risk patients. Risk stratification of patients using these factors might lead to better patient selection for the procedure, early consideration of preventive measures, deciding when to discharge the patients and perhaps referring high risk groups to more expert providers.

METHOD AND MATERIAL

In this study, all patients who underwent ERCP in our tertiary university hospital from 2013 to 2016 were identified through a cross-sectional search in our hospital database. Patients' data were collected from hospital files which included demographic data, clinical and paraclinical information including patients' comorbidities, drug history, surgical history, and laboratory data), sonographic findings, ERCP details and results. Patients meeting the criteria for PEP by Cotton *et al* [3] were identified and the severity of PEP was determined.

According to this reference, PEP was defined as abdominal pain suggestive of pancreatitis requiring new hospitalization or extension of hospital stay and a serum amylase at least three times the upper limit of normal, 24 hours after the procedure [3]. Needed hospital stay defines the grading of PEP with mild for 2-3 days of hospital stays and moderate for 4-10 days of hospital stay. Severe post-ERCP pancreatitis is defined as the need for a hospital stay longer than 10 days, or by the development of a complication such as necrosis or pseudocyst, or need for intervention (drainage or surgery) [3].

Data from PEP patients were compared to the rest and the results were analyzed using SPSS. Categorical and dichotomous variables were assessed by χ^2 tests or Fischer's exact test when necessary. Continuous variables were assessed using either two sample t-tests. A p value <0.05 was considered significant. Technical/operator and endoscopy-related variables were unchanged during the three-year study period.

RESULTS

After excluding incomplete patient files, data from a total of 462 patients was included in the final analysis. Study population consisted of 200 women and 262 men with mean

age of 59.1 ± 0.59 (age range: 21-92 years). Of this group, 24% were smokers, 14.7% were addicted to some sort of narcotics and 3.7% gave a history of alcohol use.

Frequency of concomitant medical conditions in descending order included hypertension, ischemic heart disease, diabetes mellitus, cancers other than biliary-pancreatic, inflammatory bowel disease and cirrhosis. Characteristics and medical history of study population is summarized in table 1. Drug histories were incomplete in many patient files thus many drugs were excluded from analysis due to high missing data; however, at least one-year history of ASA, statins and ACE inhibitors was recorded in 29%, 19.5% and 11% of the patients, respectively and these medications were analyzed.

Sonographic records showed concomitant gallbladder stone in 39% of the patients. Mean CBD diameter was 10.5 mm. Fatty liver was detected in 31% of the patients. Mean CBD diameter and simultaneous gallbladder stones in sonography did not differ between PEP patients and the rest, however detection of fatty liver in sonography was significantly associated with higher incidence of PEP ($P=0.04$).

Of the total 462 ERCP procedures, 62% were successful, 25.5% were partially successful and 9.5% failed. A total of 181 cases (39.2%) had difficult cannulation from which 35 encountered a failed cannulation and in 22 cases a pancreatic stent was placed. Precut and balloon dilatation were performed in 22% and 54% of the cases, respectively. Final diagnosis was found to be CBD stone in 75% of the cases, malignancy in 24% (including pancreatic cancer, cholangiocarcinoma and carcinoma of the ampulla of Vater) and remained undetermined in the rest 1%.

Of the study population, 24 patients met the criteria for PEP (incidence of 5.2%) among whom 19 were mild, 4 were moderate and 1 was severe. Of the PEP cases, 18 had difficult cannulation. Statistical analysis found no relation between age and gender with the incidence of PEP. Moreover, history of smoking, alcohol and narcotic use showed no relation with PEP. Neither history of previous chronic medical conditions nor total number of these concomitant diseases were related to PEP and its severity. History of statin consumption was associated with lower incidence of PEP, although this relation did not reach the statistical significance ($P=0.07$).

Liver enzymes (AST and ALT) were significantly higher among PEP patients ($P=0.004$). However, ESR, CRP and LDH level didn't differ significantly between PEP patients and the rest. Higher cholesterol was associated with higher incidence of PEP, but the relationship did not reach statistical significance. Creatinine level was significantly lower among PEP group ($P=0.03$). Table 2 summarizes patients' pre-ERCP laboratory parameters.

Regarding procedure-related factors, difficult cannulation was significantly associated with PEP ($P<0.001$). There was no relationship between sphincterotomy, precut, brush

cytology and the incidence of PEP. Balloon dilatation was significantly related with PEP ($p=0.001$).

None of the studied variables were found to have a significant effect on the severity of PEP.

DISCUSSION

In this study we investigated the incidence of PEP and its associated factors as the most common complication of ERCP. Incidence of PEP in our study was 5.2% which was lower than the incidence rate of 9.9% in Asia reported in Kochar's meta-analysis [5]; however, it was comparable to several other studies including Freeman 1996 (5.4%), Wang in 2009 (4.31%) and Freeman 2001 (6.7%) [1, 10, 17].

Age range in our study was very wide (21-92) and approximately 53% of our study population were older than 60. In contrast to several previous studies which found younger age and female gender as risk factors for PEP [9, 10, 13, 17-19], our results showed no such relation. Of the 24 PEP patients in our study, 15 were men and mean age of the PEP patients was 55.7 ± 0.66 .

Among other patient-related factors, cigarette smoking has been found as a protective factor against PEP in a previous study [19]; however, we found no difference regarding this factor. In this same study [19] chronic liver disease was also found protective for PEP. In our study frequency of chronic liver disease was 3.6% and PEP occurred in none of them; however, there was no significant relation. On the other hand, chronic kidney disease (but not end stage renal disease) in our study was accompanied with lower incidence of PEP ($P=0.07$).

Preventive measures that can reduce the risk of PEP have been also widely studied. Several pharmacological agents have been studied to prevent PEP with the rationale that these interventions can interrupt with the pathophysiological cascades leading to PEP. The most highly studied medical management to reduce PEP is administration of rectal non-steroidal anti-inflammatory agents (NSAIDs) in high-risk patients [20-22]. Other studied medical agents with more conflicting uncertain results include nitrates [23-26] and somatostatin and its synthetic analogue, octreotide [27-29]. Obviously aggressive hydration remains the main evidence-based treatment of acute pancreatitis from any cause including PEP [19].

Unfortunately, due to the retrospective nature of our study and the limitations of data gathering from scanned patient files, missing data for several variables was too high to analyze particularly drug history. However, ASA, statins and ACE inhibitors were best documented.

A history of statin use was associated with lower incidence of PEP in our study although the relation did not reach significance ($P=0.07$). Consistently, we found that fatty liver

is significantly associated with higher incidence of PEP ($P=0.04$), although mean triglyceride and cholesterol levels did not significantly differ between PEP patients and the rest. This finding might be partially explained by pancreatic steatosis and possible presence of a concomitant condition in these patients known as non-alcoholic fatty pancreatic disease (NAFPD). In this disease, deposition of fat in pancreas results in inflammation and worsen the outcome of pancreatitis, which might justify the increase of PEP in these patients. Pancreatic steatosis can be confirmed on ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI). In addition, NAFPD is correlated with metabolic syndrome and obesity. Unfortunately, body mass index was a missing data in most of our patient files and thus we weren't able to analyze this important variable. Further large scale clinical trials using these modalities to confirm the relation between the presence of pancreatic steatosis and risk of PEP and also the role of metabolic syndrome in this relation are highly recommended.

Interestingly, there is a multi-center clinical trial design based on this finding hypothesizing that atorvastatin use is protective for PEP. Given the safety and availability and low price of this drug, and the possible effect on fat deposition in body, results of this RCT are very valuable in prevention of PEP [30].

Although not confirmed in many other studies, a normal bilirubin level before ERCP was found an independent risk factor for PEP in Freeman's study [17]; however, in our study bilirubin level and liver enzymes were not significantly different between PEP cases and the rest of the patients. Among other laboratory data, a previous study in our hospital on ERCP patients from 2008 to 2012 found higher ESR level as a risk factor for PEP, which was not confirmed in our study [31].

Among procedure-related risk factors of PEP, in consistent with most previous studies difficult cannulation was found a significant risk factor for PEP so that of our 24 cases of PEP, 18 had difficult cannulation. Of the total 181 cases with difficult cannulation in our study, pancreatic stent was placed in 22 patients. PEP occurred in none of the cases with pancreatic stent. Despite the rather high number of difficult cannulations in our study, PEP incidence was low which might be partially due to routine use of rectal NSAIDs after ERCP procedures as a standard protocol in our center.

Precut was performed in 22% of our procedures. Some previous studies have found precut to be associated with an increase in PEP incidence; although it seems that this relation is more due to the previous difficult cannulation leading to precut rather than precut itself [32, 33]. In our study precut was not associated with PEP, instead balloon dilatation was found significantly related with higher PEP incidence. Unfortunately, the size of the balloon used was not mentioned in many ERCP reports. Several previous studies have shown that large balloon dilatation can result in higher complication

rates including PEP, although there is no consensus [34-38].

CONCLUSION

In our study pathologic diagnosis of the disease was not related to PEP. Of the 24 cases of PEP, 2 were malignancies and the rest were CBD stones. None of the studied variables were associated with the severity of the PEP. Due to the retrospective nature of the study and data record limitations, analysis of some variables was not possible. Additionally, our small study population and low incidence of PEP made it impossible to investigate the effective factors on severity of PEP. But we came across some new interesting related variables including fatty liver as a possible risk factor and statins as possible protective factors that need to be further studied through large scale clinical trials.

Conflict of interest:

The authors declare that they have no conflicts of interest.

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Table 1: Characteristics and medical history among patients undergoing ERCP, with or without PEP

	With PEP (n=24)	Without PEP (n=438)	Total (n=462)	P-value
Male gender	15 (62)	246 (56)	261	0.79
Age (years)	54.9±17.7	59.3±16.1	59.1±0.75	0.19
Diabetes mellitus	3 (12.5)	79 (18)	82 (17.7)	0.35
hypertension	5 (20)	122 (27.8)	127 (27.5)	0.31
Ischemic heart disease	3 (12.5)	87 (19.8)	90 (19.5)	0.27
Inflammatory bowel disease	1 (4.1)	11 (2.5)	12 (2.6)	0.47
Cancer (other than pancreatobiliary)	0	36 (8.2)	36 (7.8)	0.13
cirrhosis	0	9 (2)	9 (1.9)	0.61
Fatty liver	13 (54)	131 (29)	144 (31.2)	0.04
cholecystectomy	6 (25)	184 (42)	190 (41.1)	0.07
Cigarette smoking	7 (29)	105 (23.9)	110 (23.8)	0.47
Alcohol use	1 (4.1)	16 (3.6)	16 (3.5)	0.42
Opium addiction	2 (8.3)	66 (15)	68 (14.7)	0.64

Table 2: Pre-ERCP laboratory parameters among patients undergoing ERCP, with or without PEP

	PEP	Mean±SE	Total (462)	P-value
Hemoglobin	yes	12.4±0.28	11.9±0.08	0.2
	no	11.9±0.08		
White blood cells	yes	8.2±0.47	7.8±0.16	0.6
	no	7.8±0.16		
Platelets	yes	211±12	247.3±4.9	0.08
	no	249.3±5.1		
Aspartate aminotransferase	yes	163.04±32.4	63.7±3.6	0.004
	no	58.3±3.2		
Alanine aminotransferase	yes	137.5±21.1	65.5±3.2	0.004
	no	61.5±3.1		
Alkaline phosphatase	yes	637.9±94.1	497±21.3	0.12
	no	489.3±21.8		
Total bilirubin	yes	7.19±1.2	4.5±0.31	0.05
	no	4.4±0.32		
Direct bilirubin	yes	3.8±0.75	2.7±0.19	0.2
	no	2.7±0.2		
Erythrocyte sedimentation rate	yes	36.5±4.1	37.6±1.08	0.7
	no	37.7±1.1		
Creatinine	yes	.86±0.02	1.07±0.02	0.03
	no	1.08±0.02		
Triglyceride	yes	119.4±18	139.2±3.2	0.26
	no	140.3±3.2		
Cholesterol	yes	149.1±15.6	172.7±2.9	0.13
	no	174±2.9		
Lactate dehydrogenase	yes	371.2±43.4	378.9±7.1	0.8
	no	379.3±7.1		