Risk factors for post-ERCP pancreatitis : it depends on the ERCP indication

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Abstract

Background and aims **: Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive modality, and has a high risk of causing post-ERCP pancreatitis (PEP). Risk factors of PEP have been investigated and conflicting results are present for most risk factors. The aim of this study was to evaluate the risk factors for PEP and to determine whether the risk factors differ due to the ERCP indication.**

Patients and methods **: A retrospective study was conducted which included 666 patients with 968 ERCP procedures. Some risk factors were evaluated for PEP, and they were also evaluated separately for patients with bile duct stones and patients who underwent ERCP for other reasons than bile duct stones.**

Results **: In patients with bile duct stones detected on ERCP ; female gender, lower diameter of the common bile duct, placing a biliary plastic stent and not having a cholecystectomy history were risk factors for PEP, whereas in patients without bile duct stones the only risk factor for PEP was not having a prior endoscopic sphincterotomy.**

Conclusions **: Our study revealed that PEP risk factors depend on the indication of ERCP. To the best of our knowledge our study is the first study defining cholecystectomy as a protective factor for PEP in patients with bile duct stones and endoscopic sphincterotomy history as a protective factor for PEP in patients without bile duct stones. Our study also showed that female gender, lower diameter of the common bile duct and placing a plastic biliary stent were risk factors for PEP in patients with bile duct stones.** (Acta gastroenterol. belg., **2020**, 83, **598-602**).

Key words : biliary stenting, cholecystectomy, endoscopic retrograde cholangiopancreatography, post-ERCP pancreatitis.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a frequently used invasive treatment modality for pancreaticobiliary diseases, which has various complications. Post-ERCP pancreatitis (PEP) is the most frequent complication of ERCP (1), with different reported incidence rates. In 3 studies involving more than 10000 procedures the incidence of PEP was reported 3.5%, 4.2% and 9.7% (2-4). Most of the PEPs are mild and moderate, and severe PEP accounts less than 10% (1,4,5). The identification of risk factors for PEP is important. In patients with high risk for PEP, ERCP should be avoided, or methods to reduce the probability of PEP -pancreatic stent placement for example- could be performed during ERCP.

Risk factors for developing PEP have been investigated in many studies for years and a meta-analysis defined ten risk factors for PEP : female gender, previous pancreatitis history, previous PEP history, Sphincter of Oddi dysfunction, intraductal papillary mucinous neoplasm, difficult cannulation, endoscopic sphincterotomy, precut sphincterotomy, pancreatic stent placement and main pancreatic duct injection (6). There is still controversy about some risk factors. For example younger age (7), periampullary diverticulum (8), normal serum bilirubin level (9), absence of common bile duct stones (10) are previously reported risk factors for PEP, but these parameters showed no statistically significant difference in predicting PEP in the aforementioned meta-analysis (6).

The aim of this study was to evaluate retrospectively risk factors for PEP, and to evaluate whether the risk factors differ in patients whose ERCP was performed for bile duct stones and other reasons than bile duct stones.

Materials and methods

We investigated retrospectively patients who underwent ERCP at the department of Gastroenterology between December 2012 and December 2015. Patients who underwent ERCP with the aim of pancreatic cannulation were not included in the study. Between this time period 1053 procedures were performed in 741 patients (Fig.1). Among these patients 32 were excluded from the study because of insufficient data. The patients' demographic features, endoscopic and laboratory findings were investigated retrospectively. The endoscopic and laboratory data was obtained from the recorded computerized database.

All patients signed written informed consent for ERCP before the procedure. All ERCP procedures were performed by two endoscopists using 4.2- mm channel adult type therapeutic Exera CLV-160 model Olympus duodenoscopes (Olympus Medical Systems Corp. Tokyo, Japan). Topical anesthesia was administered with 10% lidocaine spray. The ERCP procedures were made under conscious sedation which was achieved with intravenously administrated propofol or midazolam, and to slow intestinal motility Hyoscine N-butylbromide was used. Guidewire cannulation was used in all patients.

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Endoscopic sphincterotomy for the removal of stones was performed and other therapeutic procedures -mechanical lithotripsy, bile duct stent placement and dilation, brush cytology- were performed when indicated.

Serum amylase and lipase levels were measured at 2-4 h and 24 h after the procedure. PEP was defined as elevated amylase level greater than 3 times the upper normal limit for more than 24 hours after the ERCP procedure with hospitalization need for more than one night (11).

The local Medical Ethics Committee approved the study design and methods.

All statistical analyses were performed with the SPSS 20.0 software. Independent Samples T-Test was used to determine the differences in variables. The Pearson Chi-square test was used to compare categorical variables between groups. P values of less than 0.05 were considered as significant. Univariate analysis with chi-square test for categorical variables was performed and significant predictors were included in a multiple logistic regression model to identify risk factors for PEP and calculate odd's ratios (OR). OR with 95% confidence interval (CI) were calculated.

Results

Within the time period this study was performed, 741 patients underwent 1053 ERCP procedures. Among these patients 32 patients were excluded from the study for insufficient data and 43 patients were excluded who underwent ERCP for indications which needed pancreatic duct cannulation. The statistical analysis included 666 patients with 968 procedures (Fig. 1). The mean ERCP procedure per patient was 1.45 (1-6 procedure per patient). The study included 310 (46.5%) men and 356 (53.5%) women and the mean age of the participants was 61.96±17.25 (range :18-92).

The overall PEP incidence was 8.2%. Statistically significant risk factors for PEP were having a common bile duct diameter less than 12 mm and placing a plastic biliary stent during ERCP, whereas having cholecystectomy or EST history reduced the risk of PEP (Table 1). The gender and age had no influence on the risk of PEP in the whole population (Table 1). The mean common bile duct diameter was 12.45±4.12 in patients with cholecystectomy, and 11.63±4.21 in patients without cholecystectomy (p :0.005).

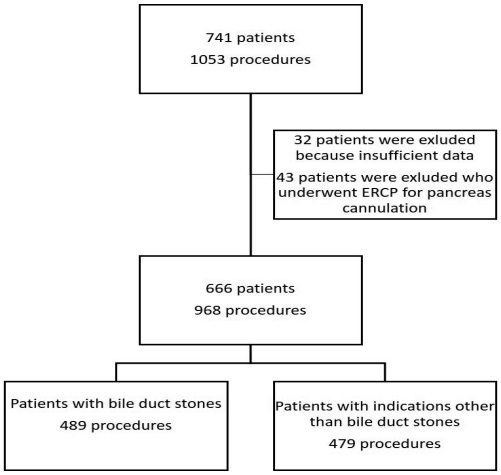

Fig 1. The study flowchart. A total of 741 patients with 1053 procedures were screened, and 75 patients were excluded from the study. The indications for ERCP were bile duct stones in 489 procedures, and other reasons than bile duct stones in 479 procedures.

Among the 968 procedures 489 procedures were performed for bile duct stones and 479 procedures were performed for other reasons (Fig. 1). Patients who had malignant or benign strictures with bile duct stones were included in the non-bile duct stones group. The total successful cannulation rate was 91.6%, whereas it was 94.5% and 86.7% for patients with and without bile duct stones, respectively. The group including patients other than bile duct stones, the indications for ERCP were as follows : Pancreaticobiliary malignancies :246, benign bile duct strictures : 173, post cholecystectomy leakage :41, rupture of echinococcus cysts into the bile ducts :8, fasciola hepatica :4, choledochal cysts :5, post-transplantation biliary strictures :2. Of the patients who underwent ERCP for bile duct stones, stone was detected during ERCP in 91.9% of the patients and it could be extracted successfully in 76.5%.

The data of patients with bile duct stones and other indications than bile duct stones were evaluated separately for the effect of age, cholecystectomy or EST history, gender, placing a biliary plastic stent and common bile duct diameter on PEP. In patients with bile duct stones

Table 1. — **The PEP incidence and the number of PEP and ERCP procedures [PEP incidence% (PEP/ERCP procedures)] in the whole study group**

	PEP incidence (No. of PEP/ No. of ERCP procedures)		P value
	Present	Absent	
Female gender	9.7% (50/514)	6.4% (29/454)	0.058
Age <65 years	8.9% (41/462)	7.5% (38/506)	0.439
Common Bile duct diameter <12 mm	10.2% (50/492)	6.1% (29/476)	**0.021**
Prior cholecystectomy	5.4% (16/294)	9.3% (63/674)	**0.041**
Prior EST	5.7% (19/335)	9.5% (60/633)	**0.040**
Placing a biliary plastic stent	11.0% (32/290)	6.9% (47/678)	**0.033**

ERCP : Endoscopic retrograde cholangiopancreatography, EST : endoscopic sphincterotomy, PEP : Post-ERCP pancreatitis

Table 2. — **The PEP incidence and the number of PEP and ERCP procedures [PEP incidence% (PEP/ERCP procedures)] in patients with and without bile duct stones**

		PEP incidence (No. of PEP/ No. of ERCP procedures)		P value
		Present	Absent	
Patients with bile duct stones	Female gender	10.7% (29/272)	5.5% (12/217)	**0.042**
	Age <65 years	9.0% (20/223)	7.9% (21/266)	0.670
	Common Bile duct diameter <12 mm	12.9% (29/224)	4.5 % (12/265)	**0.001**
	Prior cholecystectomy	4.0% (6/151)	10.4% (35/338)	**0.019**
	Prior EST	7.8% (13/166)	8.7% (28/323)	0.752
	Placing a biliary plastic stent	13.8 % (13/94)	7.1% (28/395)	**0.034**
Patients without bile duct stones	Female gender	8.7% (21/242)	7.2% (17/237)	0.542
	Age <65 years	8.8% (21/239)	7.1% (17/240)	0.490
	Common Bile duct diameter <12 mm	7.8% (21/268)	8.1% (17/211)	0.929
	Prior cholecystectomy	7.0% (10/143)	8.3% (28/336)	0.619
	Prior EST	3.6% (6/169)	10.3% (32/310)	**0.009**
	Placing a biliary plastic stent	9.7% (19/196)	6.7% (19/283)	0.235

ERCP : Endoscopic retrograde cholangiopancreatography, EST : endoscopic sphincterotomy, PEP : Post-ERCP pancreatitis.

detected on ERCP; female gender, lower diameter of the common bile duct, placing a biliary plastic stent during the procedure and not having a cholecystectomy history were risk factors for PEP, but not in the patients without bile duct stones (Table 2). On the contrary, having a prior EST was a protective factor from PEP in patients without bile duct stones, but not in patients with bile duct stones (Table 2).

Multivariate analysis was performed and gender, age, placing a biliary plastic stent, the bile duct diameter before ERCP, EST history and cholecystectomy history were included in the analysis. Significant risk factors for PEP were as follows : female gender (OR:1.85, 95% CI:1.13-3.03, P=0.014), placing a biliary plastic stent during the procedure (OR:2.20, 95% CI:1.33-3.64, P=0.002), not having a prior EST history (OR:1.86, 95% CI:1.06-3.26, P=0.031) and having a common bile duct diameter less than 12 mm (OR:1.67, 95% CI:1.02-2.75, P=0.044). Multivariate analysis with the same parameters was performed separately for patients with bile duct stones and other indications. Statistically significant risk factors for PEP in patients with bile duct stones were female gender (OR:2.86, 95% CI:1.37-6.02, P=0.006), not having a prior cholecystectomy history (OR:2.88, 95% CI:1.12-7.41, P=0.028), placing a biliary plastic stent during the procedure (OR:3.61, 95% CI:1.57-8.26, P=0.002) and having a common bile duct diameter less than 12 mm (OR:3.87, 95% CI:1.77-8.43, P=0.001). In patients without bile duct stones the only statistically significant risk factor for PEP was not having a EST history before the ERCP (OR:3.57, 95% CI:1.43-8.91, P=0.007).

Discussion

ERCP is an invasive procedure with different complications, and PEP is the most prevalent one (1,12). Its incidence varies from study to study probably because of the case differences and the different diagnostic criteria for defining PEP (13). Although it is generally a mild condition, PEP may present with severe disease and mortality may occur, and it prolongs the total time of hospitalization. Because of these reasons, it is important to predict the risk of PEP before ERCP to give decision to perform ERCP, or to perform methods to reduce the probability of PEP.

Our study showed that lower diameters of the common bile duct and placing a biliary plastic stent during the ERCP procedures were risk factors for PEP, whereas the prior history of cholecystectomy and EST reduced the risk of PEP. After multivariate analysis the cholecystectomy history lost its significance, but no EST history, placing a biliary stent and lower common bile duct diameter were still statistically significant risk factors for PEP.

Although some studies have shown no increased risk of PEP in female gender (14-16), most studies found it as a risk factor for PEP (6,8,9,17). The increased risk of PEP in female patient was attributed to the higher frequency of biliary stones and SOD (6). Our data does not support this hypothesis because when only patients with bile duct stones were included in the analysis, women with bile duct stones had a higher incidence of PEP compared to men. This statistically significant result was not obtained in the whole population. With these findings we can say that female gender is a risk factor for PEP in patients with bile duct stones but not in patients whose ERCP was performed for other reasons.

Age was not a risk factor in our study in the whole group and in patients with and without bile duct stones. Higher PEP incidence in younger persons have previously been described (8,18), but the majority of studies have shown no increased risk for PEP in younger individuals, like our study (6,19,20).

It's not certain whether the common bile duct diameter has an effect on PEP. Some studies showed higher PEP incidence in patients with narrower bile ducts (8,21), whereas some showed no difference in PEP due to common bile duct diameter (9,22,23). Our study showed

that having a common bile duct lower than 12 mm was a risk factor for PEP. But in patients whose ERCP was performed for other indications than bile duct stones it was not a risk factor for PEP.

Performing EST during ERCP has increased risk for PEP development (6,24), but formerly performed EST history showed no effect on PEP in some studies (9,25). Our study showed that formerly EST history was a protective factor for PEP. Interestingly PEP was lower in patients with EST history whose ERCP was performed for reasons other than bile duct stones, but not in patients with bile duct stones. The different outcomes of EST history on PEP in patients with and without bile duct stones was not previously published.

Our study showed lower PEP incidence in patients who had a prior cholecystectomy history. The statistical significance was lost in the multivariate analysis in the whole group, but it was found as a protective factor for PEP in the multivariate analysis performed with the patients whose ERCP was performed for bile duct stones. This data is not in accordance with the existing literature. Some studies showed increased PEP incidence in patients with cholecystectomy (9,17,26). In two of these studies cholecystectomy was a risk factor in univariate analysis, but lost significance in the multivariate analysis. There is also data that cholecystectomy has no effect on PEP (8). To the best of our knowledge our study is the first report defining cholecystectomy history as a protective factor for PEP, in patients whose ERCP was performed for bile duct stones. The exact mechanism why cholecystectomy protects against PEP is not well known. Patients with prior cholecystectomy have wider common bile duct diameters (27), and narrow bile duct diameter is a risk factor for PEP. This may be an explanation about the effect of cholecystectomy on PEP, but after multivariate analysis cholecystectomy was still a protective factor in patients with bile duct stones, and this shows that the effect of cholecystectomy on PEP risk cannot be explained with this mechanism. Further studies are needed to evaluate the interaction between cholecystectomy and PEP.

The discrepancy between different studies about risk factors for PEP may be due to our findings that PEP risk factors depend on the indications for ERCP. The indications for ERCP differ between centers, and this difference may lead to different results about the risk factors for PEP.

A limitation of the study was the retrospective design and a prospective design could give better results. Another limitation is that some of the patients received no routine rectal administration of diclofenac or indomethacin. Because most of the procedures were performed before the recommendation of routine administration of these drugs before or after ERCP in all patients, which was advised by the ESGE guideline (1). We could not evaluate the effect of rectal diclofenac or indomethacin on PEP, because of the retrospective design of the study and inadequate data. Another limitation of our study was the relatively high overall PEP incidence. The rate of PEP depends on operator skills and experience. Our post ERCP pancreatitis ratio is higher than excepted, and this is probably due to the experience of our center. Another reason is that at the time period this study was performed routine administration of rectal diclofenac or indomethacin and pancreatic stent placement was not performed at our institution.

Conclusion

Our study showed that risk factors for PEP vary according to the indication of ERCP. Female gender, not having prior cholecystectomy history, placing a biliary stent during the procedure and having a common bile duct diameter less than 12 mm were risk factors for PEP in patients with bile duct stones. The only risk factor for PEP in patients who underwent ERCP for other indications than bile duct stones, was having a naive papilla. To the best of our knowledge our study is the first study defining cholecystectomy and EST history as protective factors for PEP in patients with and without bile duct stones, respectively. These new findings about PEP risk factors should be investigated in further studies with larger study populations.

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