Risk factors for post-ERCP pancreatitis: a prospective multicenter study in upper Egypt

Mohammed A. Omar[a], Ahmed E. Ahmed[a], Omar A. Said[a], Hussein El-Amin[b]

[a]Department of General Surgery, Faculty of Medicine, Sohag University, Sohag
[b]Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Mohammed A. Omar, MD, Department of General Surgery, Faculty of Medicine, Sohag University, 82511 Sohag, Egypt
Tel: (002) 0965228628; fax: (002)0934602963; e-mail: elqefty@yahoo.com

Received 27 May 2014
Accepted 02 September 2014

The Egyptian Journal of Surgery
2015, 34:1–10

Background and study aims
Endoscopic retrograde cholangiopancreatography (ERCP) has become widely available for diagnosis and treatment of pancreatic and biliary diseases. Pancreatitis is the most common and serious complication to occur after ERCP resulting in substantial morbidity and occasional mortality. The aim of this study was to evaluate the potential patient and procedure-related risk factors for postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) in a prospective multicenter study.

Patients and methods
Consecutive ERCP procedures were prospectively studied at five centers (two universities, three private). Data were collected on patient characteristics and endoscopic techniques before the procedure, at the time of procedure, and 24–72 h after discharge. PEP was diagnosed and its severity graded according to consensus criteria.

Results
Pancreatitis occurred after 104 (8.9%) of 1162 consecutive ERCP procedures and was graded mild in 66 (63.5%), moderate in 30 (28.8%), and severe in eight (7.7%) cases. On univariate analysis, 11 of 18 evaluated variables were found to be significantly associated with PEP. On multivariate analysis, significant risk factors with adjusted odds ratio (OR) were: difficult cannulation (OR: 10.2), previous PEP (OR: 8.1), previous pancreatitis (OR: 7.9), at least two pancreatic duct injections (OR: 3.1), pancreatic duct cannulation (OR: 2.7), difficult stone extraction (OR: 2.2), and precut sphincterotomy (OR: 1.2).

Conclusion
Technique-related risk factors are probably more numerous and potent than patient-related ones in determining high-risk predictors for PEP.

Keywords:
endoscopic retrograde cholangiopancreatography, pancreatitis, risk factors

Egyptian J Surgery 34:1–10

1110-1121

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most complex endoscopic procedures [1]. The reported incidence of ERCP-specific complications ranges from 5 to 40%, depending on the complexity of the procedure, the underlying diagnosis, and the patient comorbidities [2,3].

Acute pancreatitis remains the most common and serious complication after ERCP with reported incidence ranging from 1.3 to 15.1% in most prospective series, resulting in substantial morbidity and occasional mortality [4–10]. Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is defined as acute pancreatitis that has developed de novo following ERCP [9,11]. The mechanisms that lead to PEP are complex and not fully understood. Rather than having a single pathogenesis, PEP is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, microbiologic, and thermal factors [12].

Several technical and patient-related risk factors for PEP, which act independently or together, have been identified [6,13,14]. The most previous studies of PEP have focused primarily on procedural and technical factors. However, it is equally plausible that patient characteristics also account for susceptibility or resistance to PEP [12]. The reported risk factors vary widely from study to study and these discrepancies may be attributable to differences in criteria used for diagnosis, differences in patient populations, indications, endoscopic techniques, endoscopic expertise, methods of data collection, and the use of preventative techniques such as placement of pancreatic stents [15–17]. More important, the use of univariate analysis to identify risk factors for PEP may produce misleading results because of inability to sort out confounding variables [18–22]. Recent studies have used multivariate analysis as a tool to identify and quantify the effect of multiple potentially confounding risk factors [2,4–7,23–26].

One of the most important steps to prevent PEP is to avoid the procedure altogether whenever possible, especially in patients who are thought to be at high-risk for this complication. Hence, awareness of

 DOI: 10.4103/1110-1121.153364

the risk factors for PEP is essential for the recognition of high-risk cases in which ERCP should be avoided if possible or in which protective endoscopic or pharmacologic interventions should be considered [27].

Aim of the work

The primary goal of this study was a comprehensive, prospective evaluation of risk factors for post-ERCP pancreatitis. To maximize the generalizability of the findings, groups in private practice as well as tertiary referral centers were included. This research attempted to evaluate the commonest postulated risk factors for PEP including patient and procedure-related variables, to generate a multivariate model that could identify the most important determinants of PEP for improving the safety of ERCP.

Patients and methods

This was a prospective, multicenter study conducted at five centers in Upper Egypt (three private practices, two universities-affiliated teaching hospitals). Of the 1162 consecutive patients scheduled to undergo ERCP, 712 (61.3%) were women and 450 (38.7%) were men, with a mean (± SD) age of 44.8 (± 13.9) years.

Patients were excluded for any of the following reasons:

(a) Age less than 18 years,
(b) Pregnancy,
(c) Mental disability,
(d) Patients with contraindication to ERCP (coagulopathy, history of contrast dye anaphylaxis, severe cardiopulmonary disease, recent myocardial infarction),
(e) Acute pancreatitis, cholangitis, or hyperamylasemia at the time of the procedure,
(f) Certain structural abnormalities of the upper gastrointestinal tract, which increase the risk of the procedure or renders it technically difficult or impossible, for example esophageal stricture,
(g) Planned biliary stent removal or exchange without planned ductal cannulation,
(h) Need for emergent ERCP within 12 h, or
(i) Prophylactic antibiotics. Ethical committee approval and informed written consent were taken before conducting the study at all participating centers.

All ERCP procedures were performed by high-volume endoscopists (who perform more than two sphincterotomies per week [33]. The data were collected during and after the procedure by the resident doctors who are not involved in the direct patient care and from the hospital reference sheets. All patients were admitted to the hospital at least for 24 h following the procedure to detect early complications. All patients were monitored at least for 6 h in the postoperative recovery room after the procedure to detect early symptoms and signs of pancreatitis then transferred to the inpatient department where they continue to be looked after by the resident for the rest of the 24 h until they can be discharged. Measurement of serum amylase was performed by sampling of blood at 4 h post-ERCP; if the 4 h amylase level was normal or less than three-fold increase, we repeat it on the next day before discharge. Abdominal ultrasonography was routinely performed in all patients suffering from pancreatic-like pain lasting at least 24 h for early detection of PEP. In cases of doubt of developing PEP, abdominal CT scan was performed. If complications arose, patients stayed in the hospital until they recovered.

Definitions

Bile duct diameter was the measured maximal duct diameter within 2 cm of the papilla adjusted for X-ray magnification. If any stricture was present, bile duct diameter was measured proximal to the stricture [9,11]. Cannulation time was measured between the time when the papillotome was advanced out of the endoscope channel, in front of the papilla, and the time when successful deep cannulation was evidenced by injection of contrast [11]. Total procedure time was measured between the time when the endoscope was advanced in the mouth and the time when the endoscope was advanced out from the mouth [11]. The number of pancreatic duct contrast injections was the total number of times when any volume of contrast was injected into the pancreatic duct [11]. Pancreatic cannulation was defined as deep cannulation of the pancreatic duct with any device [8]. Successful cannulation was defined as free and deep instrumentation of the biliary tree. A cannulation attempt was defined as sustained contact between the cannulating device and the papilla for at least 5 s [28]. Difficulty of cannulation was determined on the basis of the number of attempts on the major papilla with a cannulation instrument before final: easy (one to five attempts); moderate (six to 15 attempts); and difficult (>15 attempts) [9]. Difficulty of stone extraction was classified into three degrees: easy (Grade 0), stone extraction with no resistance; moderate (Grade 1), stone extraction with some resistance; difficult (Grade 2), stone extraction after lithotripsy or failed stone extraction.

The generally accepted criteria for the diagnosis of PEP were proposed in 1991 during a consensus workshop [13]. These criteria include the new onset

of pancreatic-type abdominal pain associated with at least a three-fold increase in serum amylase or lipase occurring within 24 h after an ERCP, and the pain symptoms need to be severe enough to require admission to the hospital or to extend the length of stay of patients who are already hospitalized [17]. Amylase values have been found to peak between 90 min and 4 h post-ERCP [29]. The serum amylase level measured 4 h after the procedure is the most reliable predictor of PEP [30,31]. We therefore used the 4 h amylase level as the most accurate amylase value for predicting subsequent pancreatitis. The severity of pancreatitis was classified on the basis of the length of hospital stay (2–3 days = mild; 4–10 days = moderate; >10 days or complications as hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or a need for percutaneous drainage or surgery = severe) [9,13]. Hyperamylasemia was defined as an increase of serum amylase to greater than the upper limit of normal [32].

Statistical analysis

The primary outcome analyzed was development of PEP. Analysis of risk factors was performed as follows: 18 potentially relevant risk factors were assessed by univariate analysis with the χ^2-test for categorical variables and simple logistic regression for continuous variables. A two-tailed *P* value of less than 0.05 was considered significant. Significant univariate predictors were then included in a forward stepwise multiple logistic regression model to identify the most important risk factors for pancreatitis. Goodness-of-fit for the final multivariate model was assessed by the two-log likelihood criterion.

Results

This was a descriptive single-arm prospective study that included 1162 patients subjected for ERCP between June 2009 and June 2013 (Table 1). ERCP was carried out to all patients (1162); cannulation of the papilla of Vater was successful in 1124 patients (96.7%) and failed in 38 patients (3.3%), 20 cases after trials of standard cannulation and 18 cases after precut sphincterotomy (Table 2).

The patient-related risk factors that were evaluated for PEP are: age, sex, previous pancreatitis, previous PEP, previous cholecystectomy, previous sphincterotomy, total serum bilirubin, common bile duct (CBD) diameter, and nature of the disease. The technique-related risk factors that were evaluated for PEP are: total procedure time, cannulation time, degree of difficulty of cannulation, number of pancreatic duct cannulation, number of pancreatic duct injection, biliary sphincterotomy, precut sphincterotomy, balloon dilatation, and degree of difficulty of stone extraction.

Table 1 Indications for endoscopic retrograde cholangiopancreatography

Indications	*n* (%)
Choledocholithiasis	802 (69)
Cholangiocarcinoma	104 (9)
Benign biliary stricture	82 (7)
Cancer head of pancreas	74 (6.4)
Ampullary tumor	42 (3.6)
Suspected SOD	32 (2.8)
Postoperative biliary leakage	18 (1.5)
Choledochocele	8 (0.7)

Table 2 Causes of failed cannulation

Causes	*n* (%)
Small and stenosed papilla	20 (1.7)
Duodenal diverticulum	10 (0.9)
Ampullary tumor	8 (0.7)

Serum amylase level was estimated 4 h after ERCP, and accordingly patients were divided into three groups:

(a) Patients with no hyperamylasemia (normal serum amylase level),
(b) Patients with hyperamylasemia (serum amylase level less than three times the upper limit of normal=asymptomatic hyperamylasemia), and
(c) Patients with hyperamylasemia (serum amylase level equal to or greater than three times the upper limit of normal = acute pancreatitis).

Upon studying patients after ERCP, 290 patients (25%) had no hyperamylasemia, 768 patients (66.1%) had asymptomatic hyperamylasemia, and 104 patients (8.9%) had acute pancreatitis [Assiut University Hospital 54 patients (9.1%), Sohag University Hospital 22 patients (8.2%), and the private centers: 10 (8.5%), 9 (8.7%), 9 (11%)]. All patients with an increase of serum amylase of three folds or more had epigastric pain radiating to the back persistent for 24 h (acute pancreatitis).

Upon studying patients with PEP according to the length of hospital stay, PEP was mild in 66 patients (63.5%), moderate in 30 patients (28.8%), and severe in eight patients (7.7%). Pancreatitis-related median hospital stay was 2.9, 9.5, and 17.5 days for mild, moderate, and severe disease, respectively. The PEP-related mortality rate was 1.9% (two cases) due to severe acute pancreatitis. No deaths were reported for mild or moderate pancreatitis.

Univariate analysis

Of 18 evaluated risk factors for PEP, 11 risk factors were found to be significantly associated with

PEP: four patient-related risk factors (age, female sex, previous pancreatitis, and previous PEP) and seven procedure-related risk factors (difficult stone extraction, difficult cannulation, pancreatic duct cannulation, ≥2 pancreatic duct contrast injections, precut sphincterotomy, cannulation time, and total procedure time) (Tables 3 and 4).

Multivariate analysis

The variables found to be significant in univariate analyses were taken as candidate explanatory variables in a multivariate logistic regression analysis to identify those risk factors associated with an increased risk for PEP in a multivariate setting and to estimate their independent contributions adjusted for the effects of each of the other factors. Seven risk factors were identified to be independently associated with pancreatitis; two were patient-related risk factors and five were procedure-related risk factors (Table 5).

Discussion

Acute pancreatitis remains the most common and serious complication after ERCP. Awareness of the risk factors for PEP is essential for the recognition of high-risk cases in which ERCP should be avoided if possible or in which protective endoscopic or pharmacologic interventions should be considered. Risk factors for developing PEP have been assessed in various studies and include patient and procedure-related risk factors [6].

Both PEP and asymptomatic hyperamylasemia occur because of injury to the pancreatic tissue induced by ERCP techniques, but the reason why some patients eventually develop pancreatitis and other asymptomatic hyperamylasemia remains unknown. The underlying mechanisms of the two vastly different clinical courses may include two respects: one may be attributable to the difference in the severity of the injury to the pancreas and the other to the difference in the magnitude of inflammatory response to the injury to pancreas. Asymptomatic hyperamylasemia is associated with mild injury to pancreas, perhaps without inflammatory response to pancreas. Pancreatitis may be associated with more severe injury to pancreas, meanwhile with inflammatory response to pancreas [33].

Post-ERCP hyperamylasemia was reported by many authors to be extremely common reaching up to 70% [3,6,7,15,34]. The finding of post-ERCP hyperamylasemia is attributed to maneuvers used during ERCP as manipulation of the papilla during difficult cannulation, pancreatic duct cannulation or

Table 3 Univariate analysis of risk factors for postendoscopic retrograde cholangiopancreatography pancreatitis

Variable	Pancreatitis [*n* (%)]		*P* value
	Yes	No	
Patient-related risk factors			
Significant			
Age (years)			
≤60	92 (10)	832 (90)	0.02
>60	12 (5)	226 (95)	
Sex			
Male	22 (4.9)	428 (95.1)	0.003
Female	82 (11.5)	630 (88.5)	
Previous pancreatitis			
Yes	24 (38.7)	38 (61.3)	<0.0001
No	80 (7.3)	1020 (92.7)	
Previous PEP			
Yes	10 (38.5)	16 (61.5)	<0.0001
No	94 (8.3)	1042 (91.7)	
Nonsignificant			
Previous cholecystectomy			
Yes	14 (10.1)	124 (89.9)	0.86
No	90 (8.8)	934 (91.2)	
Previous sphincterectomy			
Yes	8 (8.3)	88 (91.7)	0.55
No	96 (9)	970 (91)	
Total serum bilirubin (mg/dl)			
≤7	54 (9.9)	494 (90.1)	0.47
>7	50 (8.1)	564 (91.9)	
CBD diameter (mm)			
<5	2 (11.1)	16 (88.9)	
5–10	40 (11.2)	318 (88.8)	0.97
>10	62 (7.9)	724 (92.1)	0.74
Nature of the disease			
Benign	86 (9.1)	856 (90.9)	0.64
Malignant	18 (8.2)	202 (91.8)	
Procedure-related risk factors			
Significant			
Difficulty of cannulation			
Easy (Grade I)	26 (4.8)	314 (95.2)	
Moderate (Grade II)	46 (9.3)	448 (90.7)	0.01
Difficult (Grade III)	32 (25)	96 (75)	<0.001
Cannulation time (min)			
≤5	44 (7.1)	378 (92.9)	0.01
>5	60 (11.1)	480 (88.9)	
Total procedure time (min)			
≤30	46 (6.4)	672 (93.6)	0.006
>30	58 (13.1)	286 (86.9)	
Pancreatic duct cannulation			
Zero time	56 (5.9)	892 (94.1)	<0.0001
≥one time	48 (22.4)	166 (77.6)	
Pancreatic duct injection			
<2 injections	74 (6.9)	996 (93.1)	<0.0001
≥2 injections	30 (32.6)	62 (67.4)	
Difficulty of stone extraction			
Easy (Grade 0)	2 (1.6)	122 (98.4)	
Moderate (Grade 1)	34 (6.1)	520 (93.9)	0.04
Difficult (Grade 2)	30 (24.2)	94 (75.8)	<0.0001
Precut sphincterotomy			
Yes	24 (18.5)	106 (81.5)	0.02
No	80 (7.8)	934 (92.2)	
Nonsignificant			
Biliary sphincterotomy			
Yes	76 (8.1)	866 (91.9)	0.14
No	28 (14)	172 (86)	
Balloon sphincteroplasty			
Yes	4 (5.7)	66 (94.3)	0.46
No	100 (9.2)	938 (90.8)	

PEP, postendoscopic retrograde cholangiopancreatography pancreatitis.

Table 4 Pancreatitis rates in with respect to the number of attempts at cannulation with and without precutting

Variable	Cannulation attempts ≤15 (%)	Cannulation attempts>15 (%)	Total (%)	*P* value
Standard cannulation	60/954 (6.3)	20/78 (25.6)	80/1032 (7.8)	<0.0001
Precut cannulation	12/88 (13.6)	12/42 (28.6)	24/130 (18.5)	<0.01
Total	72/1042 (6.9)	32/120 (26.7)	104/1162 (8.95)	<0.0001

Table 5 Multivariate logistic regression analysis of factors that predict postendoscopic retrograde cholangiopancreatography pancreatitis

Characteristics	Odds ratio (95% CI)	*P* value
Previous PEP	8.1 (1.01–98.50)	0.004
Previous pancreatitis	7.9 (2.83–58.72)	0.01
Difficult cannulation		
Moderate vs. easy	3.1 (1.07–21.26)	0.04
Difficult vs. easy	10.2 (2.44–77.26)	0.004
≥2 pancreatic duct injections	3.1 (1.64–5.75)	0.0001
Pancreatic duct cannulation	2.7 (1.43–5.17)	0.0051
Difficult stone extraction	2.2 (1.49–4.24)	0.0001
Precut	1.2 (1.11–2.26)	0.01

CI, confidence interval; OR, odds ratio; PEP, postendoscopic retrograde cholangiopancreatography pancreatitis.

injection, precut sphincterotomy, balloon dilatation, and extraction of large stones. The mechanical trauma to the papilla or pancreatic sphincter during instrumentation may cause transient obstruction of outflow of pancreatic juice. In addition, subjecting the pancreatic duct to a sudden increase in pressure may be the cause of post-ERCP hyperamylasemia. Passage of common bile duct stones is also known to cause hyperamylasemia [35].

All patients who had increase in serum amylase at least three times the upper normal limit developed clinical symptoms of acute pancreatitis lasting at least 24 h. None of patients developing increase in amylase level less than three times the upper normal limit had clinically relevant acute pancreatitis. These results are in agreement with the previous authors who found out that increased amylase level at least three times the upper normal limit is predictive of acute pancreatitis [3,34,36].

The incidence of PEP ranged from 1.3 to 15.1% in most prospective series [11]. Higher rates reach up to 40% reported in certain series [3,6,7]. In our study, the incidences of PEP are still largely in agreement and comparable with the previous reports and agreed with the internationally acceptable norms; it was 8.9% of the cases (mild = 63.5%, moderate = 28.8%, and severe = 7.7%).

Younger age was associated with a high risk for pancreatitis only in the univariate analysis. This result is consistent with multiple studies showing that younger age was found to be a significant risk factor by univariate analysis but not by multivariate model [6,9,37]. There was an inverse relationship between the age and the occurrence of PEP (the younger the patient, the higher the percentage of pancreatitis). Younger age was first identified as an independent risk factor for PEP in a multicenter study in 1996 [4], and subsequently confirmed in four other multivariate analyses [23,38–40]. The higher risk may be explained by the progressive decline in pancreatic exocrine function with aging that may protect older patients from pancreatic injury [41]. In contrast, one recent study revealed that age of 60 years or less is not associated with any clinically significant risk for PEP [11]. Another study reported that age less than 25 years was a high risk factor for PEP [30]. In addition, Nishino *et al.*'s [42] study concluded that one of the patient-related risk factors was age more than 65 years.

Female sex was a significant risk factor for PEP in univariate but not in multivariate analysis, and this result is in agreement with a large multicenter study [9]. Our study disagrees with the studies reporting that female individuals appear to be at higher risk for developing postprocedural pancreatitis compared with male individuals in both univariate and multivariate analysis [6,11,14,25,43,44]. However, most previous studies have demonstrated a higher risk in patients with sphincter of Oddi dysfunction (SOD) [8,12,38], a condition that occurs primarily in women [45]. In contrast, Testoni *et al.* [37] revealed that female sex was not associated with any clinically significant risk for PEP.

Past history of pancreatitis was a highly significant risk factor for PEP, and these findings are consistent with several recent multivariate risk factor studies [2,5,14,46]. Our analysis showed that the risk in such patients was increased eight-fold [odds ratio (OR): 7.9]. In contrast, our results are inconsistent with the studies by Freeman *et al.* [4], Freeman *et al.* [6], Friedland *et al.* [47], and Testoni *et al.* [37], which revealed that history of previous pancreatitis is only a significant risk factor by univariate analysis. In addition, history of previous PEP was found to be a highly significant factor for PEP with eight-fold risk (OR: 8.1), and these findings are consistent with several multivariate risk factors studies [2,6,7,9,14,37,47]. In contrast, a recent multivariate study revealed that history of PEP was not a significant risk factor for PEP [11]. The previous two findings suggest that certain individuals have a 'reactive'

pancreas that places them at particular risk beyond that conferred by other definable risk factors [48].

History of previous cholecystectomy was found to be insignificant risk factor for PEP. This result is in agreement with a recent multivariate study [11]. In contrast, the results obtained by Freeman *et al.* [6] and Cheng *et al.* [9] showed that prior cholecystectomy is a significant risk factor for PEP in univariate but not in multivariate analysis. In addition, history of previous sphincterotomy was found to be insignificant risk factor for PEP. This result is in agreement with two multivariate studies [6,9].

No relationship was found between total serum bilirubin level and the rate of occurrence of pancreatitis after ERCP. Similarly, most studies agreed that hyperbilirubinemia is not a risk factor for pancreatitis [11]. Some studies showed that normal bilirubin level at the time of ERCP would independently increase the risk for PEP [6,7,44,46]; another one showed that normal bilirubin was not associated with any clinically significant risk for PEP [37]. None of the patients included in our study had normal serum bilirubin level at the time of the procedure.

Common bile duct diameter was insignificant risk factor for PEP. This result is in agreement with most studies that have found no independent influence of duct size on the risk for PEP [2,4,6,9,11,23,26,37–39]. In contrast, many early studies suggested small CBD diameter as a risk factor for pancreatitis [5,18,20,40]. The original descriptions of small CBD diameter as a risk factor came from centers with a preponderance of patients with sphincter dysfunction, most of whom also had nondilated bile ducts. Perhaps, small bile duct diameter has appeared to be important because it was a surrogate marker for absence of elevated serum bilirubin, presence of SOD, or female sex [6].

No significant difference was found between benign and malignant nature of the disease with respect to PEP. This result is in agreement with the only study comparing the relationship of nature of the disease and PEP [49]. The higher incidence of pancreatitis in patients with benign obstructive jaundice in comparison with patients with malignant obstructive jaundice may be attributed to gallstones (the commonest indication in patients with benign obstructive jaundice), which increases the risk for pancreatitis. Proposed mechanisms include reflux of noxious bile into the pancreatic duct from transient obstruction of the ampulla during gallstone passage and pancreatic ductal hypertension from either a stone impacted at the ampulla or ampullary trauma caused by stone passage [50]. In addition, patients with pancreatic malignancy appear to be at decreased risk for PEP, likely because of chronic obstruction of the pancreatic duct along with atrophy of the upstream pancreatic parenchyma [51].

Standard sphincterotomy was insignificant risk factor for PEP. This result is consistent with the previous data confirming that the performance of biliary sphincterotomy does not appear to add significant independent risk for pancreatitis after ERCP [2,6,7,9,26]. In certain circumstances, biliary sphincterotomy may be protective; pancreatitis occurred in four of 24 patients (17%) who had plastic biliary stents placed for hilar strictures without a sphincterotomy versus none (0%) of 59 in whom a sphincterotomy was performed, suggesting that a fulcrum effect of the proximal stricture on the large-caliber biliary stent, pushing it against the pancreatic duct orifice in the intact papilla, led to the increase in frequency of pancreatitis and that this could be precluded by biliary sphincterotomy [52].

Precut sphincterotomy was a barely significant (OR: 1.2) risk factor for PEP. There is controversy in the literature regarding the relationship of precut sphincterotomy with the occurrence of pancreatitis and other complications [53–57]. Many authors reported that precut sphincterotomy was an independent risk factor for PEP [4,5,7,11,14,37,58]. It has been controversial whether higher rates of complications and pancreatitis after precut sphincterotomy are because of the precut itself, the antecedent repeated cannulation attempts, the indication for the procedure (most risky with SOD in the absence of pancreatic stenting), other anatomic factors such as small papillas, or the thermal injury to the pancreatic sphincter causing edema and duct obstruction [59,60].

Our study also confirmed that early precut was safer than either delayed precut or multiple attempts at cannulating the papilla (6.9 vs. 25.6 and 28.6%), supporting the concept that, in expert hands, precut might be preferable to repeated cannulation attempts, especially in patients at high risk for postprocedure pancreatitis. This result is compatible with two recent meta-analyses; the first showed that PEP developed in 2.5% of patients randomized to early needle-knife sphincterotomy compared with 5.3% of patients who underwent persistent cannulation attempts before needle-knife sphincterotomy [61] and the second concluded that early needle-knife sphincterotomy significantly reduced the rate of PEP from 5.4 to 2.5% [62]. In addition, a recent retrospective study demonstrated that the rate of PEP was lower when this technique was performed with less than 10 cannulation attempts compared with 10 or more cannulation attempts without precutting [63].

In contrast, in many series from tertiary referral centers, the complication rate for precut sphincterotomy was no different than that for standard sphincterotomy [9,53,54,56,64–67], suggesting that risk for precut sphincterotomy is highly operator-dependent. In addition, this result disagree with the result of Freeman *et al.* [6] who concluded that precut access was associated with higher univariate but no independent risk for pancreatitis; however, most of these procedures were performed by a few highly experienced endoscopists and often included placement of a pancreatic stent.

Balloon dilatation of the CBD orifice for stone extraction was insignificant risk factor for PEP. This result was consistent with several studies that have demonstrated that balloon dilatation of the distal CBD and ampulla can be a well-tolerated and effective technique for the removal of biliary stones without increasing the rate of PEP [68–74]. In contrast, other studies showed that balloon dilatation has been associated with a markedly increased risk for PEP [6,75–77].

The duration of the whole procedure and the cannulation time were significant risk factors for pancreatitis in univariate but not in multivariate analysis, and this result is compatible with those obtained by two large studies [11,47]. Average ERCP and cannulation times were reported as 18 and 4 min by Penaloza-Ramirez *et al.* [78], and similar average durations of 16.5 and 3 min were determined by Sabri *et al.* [79]. Our results revealed that average ERCP and cannulation times were 28 and 5 min, and this disagreement may be explained by trainees' participation.

Difficult cannulation was the highest significant independent risk factor for PEP. More than 15 attempts at cannulating the Vater's papilla increased the risk for pancreatitis about 10-folds (OR: 10.2); interestingly, the risk rate showed a linear progression either between five or less attempts and six to 15 attempts (OR: 3.1) or between six to 15 and greater than 15 attempts (OR: 10.2). PEP had inverse relationship with the difficulty of cannulation (the higher the difficulty of cannulation, the higher the incidence of pancreatitis). Pancreatitis occurred in 4.8% of cannulation rated as easy, 9.3% of those considered to be moderately difficult, and 25% of cases when cannulation was considered difficult. The high incidence of pancreatitis after repeated attempts at cannulating, independently of pancreatic duct contrast injection, confirms that papillary edema-related and sphincter hypertension-related impairment of pancreatic drainage resulting from the extent of manipulation and repeated trauma of the papilla using guide wires and cannulation devices, rather than hydrostatic ductal and contrast agent injury, is a major factor. The fact that difficult cannulation did not reach significance as a risk factor in a study where prophylactic pancreatic stents were frequently used further confirms this [9]. These data also suggest that alternative techniques, such as precut sphincterotomy, should be adopted in cases with difficult cannulation, rather than insisting with multiple attempts, and confirm the preventive role of early precut in reducing the risk for pancreatitis, as in another study [80].

The difficulty of cannulation is not easily quantifiable and interactions with time for cannulation, method of cannulation, and number of pancreatic duct injections may occur [9]. Most studies came to similar results, namely difficulty in cannulation, which can produce papillary trauma, proved to be an independent risk factor for procedural complications and this risk should increase with the number of failed cannulations [2,4,6,9,26,37]. Although the difficulty of cannulation was all judged by the number of cannulation attempts in previous studies, the cutoff numbers vary widely, with six attempts in two studies, eight attempts in one study, and 20 attempts in another study [2,4,6,9].

Pancreatic duct cannulation was a significant risk factor in both univariate and multivariate analyses (OR: 2.7). This is most probably due to manipulation of pancreatic duct and pancreatic sphincter leading to subsequent spasm of pancreatic duct and obstruction of the flow of pancreatic enzymes. In addition, injury to the pancreatic duct and pancreatic parenchyma may cause premature activation of pancreatic enzymes leading to autodigestion of the pancreas. This finding agrees with that reported by Freeman *et al.* [6] stating that pancreatic duct deep cannulation is significantly associated with the risk for PEP.

Pancreatic duct injection (≥2) was an independent risk factor for PEP with a three-fold increase in risk (OR: 3.1), and this result is compatible with most previous reports [4,6,9,14,43,47,81]. In contrast, Wang *et al.* [11] concluded that pancreatic duct injection was significant only by univariate but not by multivariate analysis. They explained their result by the frequent use of guide wires cannulation that minimizes the unintentional injections into the pancreatic duct [11].

Difficult stone extraction was a significant risk factor by both univariate and multivariate analyses (OR: 2.6). PEP had inverse relationship with the degree of difficulty of stone extraction (the higher the difficulty of stone extraction, the higher the incidence of pancreatitis). In our study, pancreatitis occurred in 1.6% of extraction rated as easy, 6.1% of those considered to be moderately difficult, and 24.2% of cases when

extraction was considered difficult. This result may be explained by repeated trauma during trial of extraction and prolonged cannulation and procedure time.

Trainee participation has been previously evaluated in three large multicenter studies, and the result showed that it was not a significant risk factor for PEP [6,9,37]. In another report, the complications of ERCP performed solely by attending physician were not significantly different from those performed by fellows under the supervision of attending endoscopists [2]. Similarly, in our series, trainee participation did not increase the risk for PEP in univariate or multivariate analysis.

Data from this study can be used by the clinician to decide whether or not to recommend ERCP for an individual patient. Intraoperative laparoscopic cholangiography, MRCP, and EUS all have accuracy rates rivaling that of ERCP and are becoming widely available. These techniques may be preferable to ERCP for patients with equivocal evidence of biliary obstruction, especially those at high risk for PEP. If pathologic obstruction such as a stone is definitely identified by one of these methods, then conventional ERCP is indicated. If no pathologic obstruction is found, then ERCP should be avoided altogether or direct referral to a center with extensive experience with manometric and pancreatic therapeutic ERCP should be considered. These data can be used by the endoscopist to decide how an ERCP will be performed. In high-risk patients, prolonged efforts at cannulation and the use of high-risk maneuvers such as precut sphincterotomy should be avoided. The current data may also be useful with respect to studies on the use of pharmacologic agents to reduce PEP. Until a cost-effective agent that prevents post-ERCP pancreatitis is found, the primary hope for reducing the burden of morbidity from ERCP lies in knowledge of the risk factors and the understanding that this knowledge will be used in deciding whether an ERCP is necessary, and, if so, how best to perform the procedure.

Conclusion

Multivariate analysis indicates that technique-related risk factors are probably more numerous and potent than patient-related ones in the risk for PEP. All patients should be followed by 4 h serum amylase after ERCP for early identification of patients with PEP for early and adequate management. The most important risk factors for PEP are difficult cannulation, previous history of pancreatitis and PEP, pancreatic duct cannulation and injections, difficult stone extraction, and precut sphincterotomy.

Acknowledgements

Conflicts of interest

None declared.

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