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***Prospective Study***

**Post endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity**

El Nakeeb A *et al.* Post ERCP pancreatitis

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**Abstract**

***AIM***

To detect risk factors for Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and investigate the predictors of its severity.

***METHODS***

This is a prospective cohort study of all patients who underwent ERCP**.** Pre ERCP data, during procedure data, post ERCP data were collected.

***RESULTS***

The study population consisted of 996 cases. The mean age of presentation was 58.42 years (± 14.72), 454 were male and 442 were female patients. Overall, PEP occurred in 102 patients (10.2%) of the study population, eighty cases (78.4%) were of mild to moderate degree, while severe pancreatitis occurred in 22 patients (21.6%). No hospital mortality was reported for any of PEP patients during the study duration**.** Age group less than 35 years (*P* = 0.001, OR = 0.035), narrower common bile duct (CBD) diameter (*P* = 0.0001) and number of pancreatic cannulation (*P* = 0.0001) were independent risk factors for the occurrence of PEP**.**

***CONCLUSION***

PEP is the most frequent and devastating complication after ERCP. Age group less than 35 years, narrower median CBD diameter and number of pancreatic cannulation were independent risk factors for the occurrence of PEP. They are candidates for prophylactic and preventive measures against PEP.

**Key words**: Endoscopic retrograde cholangiopancreatography; Obstructive jaundice; Pancreatitis

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**Core tip:** Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most devastating and frequent complication after ERCP. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients. Age group less than 35 years, narrower median common bile duct diameter and number of pancreatic cannulation were independent risk factors for the occurrence of PEP.

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**INTRODUCTION**

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases[1]. However, ERCP is not a procedure without morbidities[2]. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP[3]. The reported incidence of PEP is around 5%[4,5]. This rate may increase up to 20%-40% in high risk patients. Although the majority of PEP are of mild degree, it can be severe and life threatening in a substantial proportion of cases[6].

Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients[1,7,8]. Being convinced with a number of patient-related risk factors, some gastroenterologists and surgeons prefer adoption of alternative management strategies to ERCP whenever possible in high risk patients. Similarly, some endoscopists try to avoid procedure-related risk factors to increases the safety of the procedure. All these factors make identification of risk factors for PEP of paramount importance for the practice of ERCP.

Many patient and procedure related factors are suggested to be associated with increased likelihood of PEP[8]. The trigger mechanism and pathogenesis for PEP remains unclear[9]. The aim of this study is to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Middle East in Egypt.

**MATERIALS AND METHODS**

This is a prospective cohort study of all patients who underwent ERCP in the duration between August 2012 and September 2014. Excluded patients were those who presented with obstructed stent, active pancreatitis, previous endoscopic sphinterotomy, biliary complications after liver transplantation, dye allergy, pregnancy and mental disability.

Patients were admitted 24 h before the procedure. Baseline laboratory assessment of liver functions, blood count and serum amylase level were done prior to ERCP. No pre ERCP treatment was used to decrease the risk of PEP pancreatitis. In our center, ERCP is performed under general anesthesia with endotracheal intubation in left semi prone position with monitoring of oxygen saturation, heart rate, and blood pressure. The procedure was performed by experienced endoscopists who had performed at least 1500 ERCPs over the last 10 years. Selective bile duct cannulation was carried out in all patients, but pancreatic duct cannulation was performed when necessary. when three or more attempts were needed due to difficulty in cannulation, precut papillotomy was selectively performed. In addition, endoscopic papillotomy for stone extraction using balloon, basket and mechanical lithotripsy, bile duct stent placement either plastic or self-expanding metallic stent, as well as brush cytology and dilation, were performed when indicted. Pancreatic duct stenting was not used to minimize PEP in our practice.

ERCP Data was recorded in a standardized manner including all potential risk factors for PEP. Patients were hospitalized for 24 h after the procedure and observed for symptoms and signs of post-ERCP complication. Complete blood picture and serum amylase level were done routinely after 6 h and 24 h.

Post-ERCP pancreatitis was defined and classified according to the consensus definition and grading system[10]. PEP was defined as new or worsened abdominal pain together with a serum amylase level at least three times normal at more than 24 h after ERCP and necessitating hospitalization for more than one night. PEP was graded according to the length of hospital stay and the need for intervention. Mild PEP pancreatitis requires hospitalization for 2-3 nights, moderate PEP required hospitalization for 4-10 nights and severe pancreatitis required hospitalization for more than 10 d, or required intervention or was complicated by pseudocyst[10].

Descriptive data were presented as means and standard deviation or medians with range according to the data distribution. Comparison of means was done by Chi-square test in categorical data or Student t test in continuous data. Difference was considered significant when P value was less than 0.05. Independent risk factors for PEP were assessed by multiple logistic regression model. Statistical analysis of the data in this study was performed using SPSS software, version 17 (Chicago, IL).

**RESULTS**

In the duration between August 2012 and September 2014, a total number of 1296 underwent ERCP in Gastrointestinal Surgical Center, Mansoura University, Egypt. The study population consisted of 996 cases after exclusion of those presented with obstructed stent (*n* = 66), active pancreatitis (*n* = 24), previous endoscopic sphinterotomy (*n* = 110), biliary complications after liver transplantation (*n* = 36), dye allergy (*n* = 10), pregnancy (*n* = 14) and mental disability (*n* = 10).

Indications for ERCP were malignant obstructive jaundice due to periampullary tumor (*n* = 460, 46.2%) and hilar cholangiocarcinoma (*n* = 2, 0.2%), calcular obstructive jaundice (*n* = 512, 51.4%), benign biliary stricture (*n* = 10, 1.0%), postcholecystectomy biliary leakage (*n* = 12, 1.2%). The mean age of presentation was 58.42 years (± 14.727). Male patients were 554 in comparison to 442 female patients with a male to female ratio of 1.3:1.

Overall, PEP occurred in 102 patients (10.2%) of the study population. Eighty cases (78.4%) were of mild to moderate degree, while severe pancreatitis occurred in twenty two patients (21.6%). The median length of hospital stay in patients with pancreatitis was 3 d ranging from 2 d to 15 d. No hospital mortality was reported for any of PEP patients during the study duration. Univariate analysis showed that patient age and narrower CBD diameter are statistically significant patient-related risk factors to be associated with occurrence and severity of PEP, while increased number of cannulation attempts and pancreatic cannulation more than 3 times were significant procedure-related risk factors associated with occurrence and severity of PEP. Indication for ERCP whether benign or malignant was not significantly associated with occurrence of pancreatitis (*P* = 0.4) but it was significantly associated with the severity of PEP (*P* = 0.009) (Tables 1 and 2).

Multivariate analysis after binary logistic regression analysis revealed that patient age group less than 35 years (*P* = 0.001, OR = 0.035), narrower median CBD diameter (*P* = 0.0001) and number of pancreatic cannulation (*P* = 0.0001) were independent risk factors for the occurrence of PEP (Table 3).

**DISCUSSION**

Post-ERCP pancreatitis (PEP) is the most common and serious complication after ERCP[8]. PEP is associated with higher morbidity and mortality beside its effect on increasing the consumption of hospital resources[11]. Identification of clinical and procedural correlates for PEP is of crucial importance in the practice of ERCP. It affects the medical decision regarding patient choice, adoption of pharmacological prophylactic measures, avoidance of procedural risk factors and determination of the time of discharge after the procedure[1,7,8]. Risk factors for PEP have been a matter of controversy and the pathogenesis of PEP is not fully understood yet[9,11]. This study reports risk factors for PEP according to the experience of a tertiary high volume surgical center in Egypt.

Despite advanced accessories and novel techniques in ERCP, complication rate after ERCP remained unchanged over the last decade[7.12]. According to previous reports, the incidence of PEP ranges from 5% to 40%. This great discrepancy in the reported rates can be attributed to heterogeneity of the definition of PEP and its grading system, variability in data collection, inclusion of diagnostic ERCP in the study and difference in expertise among endoscopists[13]. The incidence of PEP in this cohort is 10.2% with adoption of the consensus definition of PEP[10]. Mild to moderate PEP occurred in 80 patients (8%) while severe PEP occurred in 22 patients (2.2%). These ratios are concordant with data reported by previous studies[14-16].

Among different patient related risk factors, younger age and non-dilated extrahepatic biliary radicals were independent risk factors for PEP on multivariate analysis in this study. Also, using a cutoff value of 35 years to divide patients into two groups, PEP was significantly higher in the younger group by univariate analysis. Younger age has been a subject of controversy regarding its association with PEP[8]. Many studies reported insignificant relation between patient age and likelihood of PEP[2,17]. However, Freeman *et al*[18] first reported relatively younger age as a predictor of PEP on multivariate analysis. This finding was confirmed by later studies[5,16,19]. Higher incidence of PEP in younger age was explained by the aging effect on pancreatic exocrine function, smaller common bile duct diameter and the higher incidence of sphincter of Oddi dysfunction in younger age[13,16,18] .

Management of CBD stones in case of non-dilated extrahepatic biliary system represents a surgical challenge[20]. Laparoscopic transcholedochal CBD exploration mandates a CBD diameter of at least 6-8 mm[21-23]. According to many studies including this one, normal caliber CBD is associated with increased difficulty of the ERCP procedure[24-26]. However, most of recent studies reported absence of association between narrower CBD diameter and PEP[13]. Laparoscopic management for surgically fit patients with concomitant gall bladder and CBD stones in case of non-dilated CBD through transcystic CBD exploration or laparoendoscopic Rendez-vous is better to avoid or minimize the risk of PEP[21]. In case of isolated choledocholithiasis or in patients who are unfit for surgery, prophylactic measures against PEP should be adopted.

In this cohort, difficult cannulation, denoted by frequent cannulation attempts and pancreatic cannulation more than three times, was associated with more risk of PEP. The effect of pancreatic duct injection with contrast dye on PEP couldn’t be evaluated because we didn’t use the conventional contrast cannulation method. The effect of precut sphincterotomy on PEP is controversial[11]. Some authors advocate that precut sphincterotomy causes papillary oedema which retains pancreatic secretion resulting in PEP[8,24]. On the other hand, some authors indicate that precut sphincterotomy is usually preceded by difficult cannulation through the conventional approach and that the later is responsible for the development of PEP not the precut sphincterotomy itself[26]. This is supported by the finding that precut sphinctertomy was not reported as a risk factor for PEP from endoscopists who adopted precut sphincterotomy as a preferred technique from the start not just a salvage procedure after difficult cannulation through conventional cannulation methods[27]. Early precut lead to more successful cannulation rate without more hazard of morbidity after ERCP[28-33].

Risk factors for PEP have a synergetic effect[8]. Jeurnink *et al[*1] suggested that development of prognostic models and scoring systems based on various patient and procedure related risk factors will help in defining patients at the highest risk for PEP. According to this cohort, young patients (< 35 years) with narrow CBD (< 10 mm) who had shown evidence of difficult cannulation (high number of cannulation attempts or pancreatic cannulation more than three times) are candidates for prophylactic and preventive measures against PEP[28].

Despite the improvement of techniques of ERCP in recent years and increase experiences, the incidence of PEP has not decreases. and so studies to determine risk patients and prediction of severity of PEP are very important to give the risk factors prophylactic agents for prevention of PEP[34-37]. Pre-ERCP administration of rectal indometacin reduced the overall occurrence of post-ERCP pancreatitis without increasing risk of bleeding[34]. Some studies reported that the combination of a temporary prophylactic pancreatic plastic stent placed and rectal non-steroidal anti-inflammatory drugs (NSAIDs) is recommended for preventing PEP in high-risk cases[34-36]. Somatostatine can reduce the incidence of PEP but has not been routinely administrated in most of centers nor recommended by guidelines as prophylactic for PEP[36,37]. Patients at high risk PEP should be also monitored for at least 24 hours to avoid occurrence of PEP after early discharge[1,7].

Post-ERCP pancreatitis (PEP) is the most frequent and devastating complication after ERCP. PEP is associated with higher morbidity and mortality beside its effect on increasing the consumption of hospital resources. Age group less than 35 years, narrower median CBD diameter and number of pancreatic cannulation were independent risk factors for the occurrence of PEP. They are candidates for prophylactic and preventive measures against PEP

**COMMENTS**

***Background***

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to 20-40% in high risk patients. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients

***Research frontiers***

Many studies have tried to identify the risk factors pancreatitis after ERCP. Many patient and procedure related factors are suggested to be associated with increased likelihood of PEP. The trigger mechanism and pathogenesis for PEP remains unclear.

***Innovations and breakthroughs***

ERCP is not a procedure without morbidities. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients

***Applications***

 The data in this study suggested risk factors for PEP and investigate the predictors of its severity in a tertiary high volume. Furthermore, this study also provided readers with important information regarding the risk factors of PEP

***Terminology***

PEP remains the most devastating and frequent complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to 20%-40% in high risk patients.

***Peer-review***

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study is to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Egypt.

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**Table 1 Risk factors of pancreatitis *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No pancreatitis****894 (89.9)** | **Pancreatitis****102 (10.2)** | ***P* value** |
| **Patient related factors:** |
| Median age: | 60 | 48 | 0.0001 |
| Age group:< 35 > 35 | 32 (7.2)415 (92.8) | 20 (39.2)31 (60.8) | 0.0001 |
| Sex: Male Female  | 510 (57)384 (43) | 44 (43.1)58 (56.9) | 0.05 |
| Median serum bilirubin:< 2 mg% > 2 mg%  | 10.6124 (88.6)770 (90) | 12.516 (11.4)86 (10) | 0.760.72 |
| Median CBD diameter:< 10 mm > 10 mm  | 1670 (7.8)824 (92.2) | 1058 (56.9)44 (43.1) | 0.00010.0001 |
| Indication of ERCP: Malignant Benign  | 402 (45)492 (55) | 40 (39.2)62 (60.8) | 0.43 |
| Type of papilla: NormalAtrophic Pregnant Tumour Redundant JuxtadivericularSmalllong | 540 (60.4)18 (2)68 (7.6)64 (7.2)66(7.4)68 (7.6)60 (6.6)10 (1.1)  | 56 (54.9)8 (7.8)2 (2)4 (3.9)12 (11.8)16 (15.7)2 (2)2 (2) | 0.01 |
| Procedure related factors: |
| Number of cannulation attempts:Less than 5: Equal to or more than 6:  | 660 (73.9)234 (26.1) | 58 (56.9)44 (43.1) | 0.01 |
| Number of pancreatic cannulation: < 3 > 3  | 0864 (96.6)28 (3.4) | 260 (58.8)42 (41.2) | 0.00010.0001 |
| Method of cannulation:Conventional Precut | 640 (89.4)252 (90.6) | 76 (10.6)26 (9.4) | 0.7 |
| Biliary sphincter balloon dilatation:NoYes | 654 (73.2)240 (26.8) | 86 (84.3)16 (15.7) | 0.08 |

 **Table 2 Predictors of severity of pancreatitis *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mild to moderate pancreatitis (80)** | **Severe pancreatitis (22)** | ***P* value** |
| **Patient related factors:** |
| Median age: | 52 | 30 | 0.0001 |
| Age:< 35 > 35 | 26 (32.5)54 (67.5) | 14 (63.6)8 (36.4) | 0.0001 |
| Sex: Male Female  | 38 (47.5)42 (52.5) | 6 (27.3)16 (72.7) | 0.08 |
| Median serum bilirubin (mg%):< 2 mg% > 2 mg%  | 14.18 (50)72 (85.7) | 9.98 (50)14 (14.3) | 0.30.07 |
| Median CBD diameter (mm):< 10 mm > 10 mm  | 1042 (52.5)38 (47.5) | 916 (72.7%)6 (27.3%) | 0.00010.0001 |
| Indication of ERCP: Malignant Benign  | 39 (97.5)41 (66.1) | 1 (2.5)21 (33.9) | 0.009 |
| Type of papilla: NormalAtrophic Pregnant Tumour Redundant JuxtadivericularSmalllong | 3960491522 | 172203100 | 0.06 |
| Procedure related factors: |
| Number of cannulation attempts:Less than 5: Equal to or more than 6: | 46 (57.5)34 (27.5) | 12 (54.5)10 (45.5) | 0.03 |
| Median number of pancreatic cannulation: < 3 > 3  | 258 (72.5)22 (52.4) | 42 (9.1)20 (90.9) | 0.00010.0001 |
| Method of cannulation:conventional Precut | 58 (72.5)22 (52.4) | 18 (81.8)4 (18.2) | 0.07 |
| Biliary sphincter balloon dilatation:Noyes | 70 (87.5)10 (12.5) | 16 (72.7)6 (27.3) | 0.1 |

**Table 3 Multivariate logistic regression for pancreatitis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | ***P* value** | **Oddis ratio** | **95%CI for EXP(B)** |
| **Lower** | **Upper** |
| Age group | 0.001 | 0.035 | 0.005 | 0.259 |
| Age | 0.519 | 1.012 | 0.976 | 1.050 |
| sex | 0.362 | 0.143 | 0.075 | 0.270 |
| CBD diameter below 10 mm | 0.609 | 0.726 | 0.212 | 2.481 |
| CBD diameter | 0.000 | 0.612 | 0.495 | 0.757 |
| Difficult cannulation | 0.207 | 0.476 | 0.150 | 1.506 |
| Number of pancreatic cannulation below 3 | 0.117 | 0.219 | 0.033 | 1.460 |
| Number of pancreatic cannulation | 0.000 | 5.258 | 2.665 | 10.370 |
| papilla | 0.964 |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
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