

Research Article

Flat Papilla of Vater and Bleeding during Endoscopic Sphincterotomy: Two New Risk Factors for Post-Endoscopic Pancreatitis

Jamry A*

Surgical Department District Hospital, Poland

Corresponding author:** Jamry A, Surgical Department District Hospital, Surgical Office, Poland**Received:** January 01, 2021; **Accepted:** January 13, 2021; **Published:** January 20, 2021**Abstract*Objective:** To analyze the risk factors for post-endoscopic pancreatitis (PEP).**Background:** PEP occurs in 4%-42% of patients, depending on their risk factors. Over 56 risk factors were analyzed, but only 4 were found to be repeated in most studies.**Study:** A single-center retrospective study analyzing 402 consecutive patients with naïve papillae who underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) was conducted. The significance of 14 potentially new risk factors was evaluated, and it was found that they were associated with the level of bile duct stenosis, papilla anatomy, bleeding during sphincterotomy, endoscopic bleeding control, and pathological examination. Furthermore, 13 of the most frequently published risk factors were re-analyzed.**Results:** Five risk factors (containing two new ones) were significant with the following univariate and multivariate regression values: flat papilla (odds ratio [OR] 5.1, $p=0.0049$; OR 4.59, $p=0.0244$) and bleeding during endoscopic sphincterotomy (OR 3.58, $p=0.148$; OR 4.07, $p=0.0257$), and significance of the three already known risk factors was confirmed: age <40 years (OR 6.89, $p=0.0139$; OR 4.96, $p=0.0139$), common bile duct (CBD) diameter < 9 mm (OR 5.35, $p=0.0007$; OR 3.98, $p=0.0203$), and difficulty in cannulation (OR 3.2, $p=0.0298$; OR 7.72, $p=0.004$).**Conclusion:** This study reaffirms the risk of PEP associated with age, difficulty in cannulation, and CBD diameter. It also identifies two new risk factors: flat papilla and bleeding during sphincterotomy. These results suggest the need for a change in ERCP methodology in patients with these risk factors, but this finding requires confirmation in subsequent studies.**Keywords:** Acute Pancreatitis; Ampulla of Vater; ERCP Complications; Post-Endoscopic Pancreatitis Risk Factors**Abbreviations**

CBD: Common Bile Duct; ERCP: Endoscopic Retrograde Cholangiopancreatography; ES: Endoscopic Sphincterotomy; OR: Odds Ratio; PEP: Post-Endoscopic Pancreatitis

Introduction

The incidence of Post-Endoscopic Pancreatitis (PEP) ranges from 4% to as high as 42% in patients after Endoscopic Retrograde Cholangiopancreatography (ERCP), as determined risk factors that exist in individual patients [1,2]. Therefore, knowledge about the risk factors enables proper risk assessment and selection of the best treatment options. Previous studies have analyzed over 56 risk factors, but even in the most extensive studies conducted, only four of them have been repeated (sphincter of Oddi dysfunction, female sex, pre-cut incision, and unintentional contrast filling of the duct of Wirsung) [1,3-9]. Therefore, it is likely that the importance of already identified risk factors has not been clearly evaluated, and not all risk factors have been probably identified. For these reasons, the

existence of 14 new potential risk factors associated with the level of biliary stenosis, Vater's papilla anatomy, bleeding during Endoscopic Sphincterotomy (ES), endoscopic treatment of post-sphincterotomy bleeding, a biopsy of the papillae, and stent diameter in the Common Bile Duct (CBD) > 7 Fr were analyzed. Furthermore, the 13 most frequent previously studied risk factors associated with preoperative general, local, and procedure-associated conditions were re-analyzed.

Material and Methods

A single-center retrospective study was conducted to examine patients who underwent therapeutic ERCP between February 2010 and November 2011. Data were collected from Endobase (procedural details), Oracle - hospital medical database (perioperative course), and medical records from other hospitals (comorbidities). The study was approved by the Bioethical Committee at Swietokrzyska Medical Chamber (Resolution No. 11/2020 - VII). All procedures were performed by one endoscopist while complying with the commonly used ERCP protocols. Difficult cannulation was defined

as unsuccessful access to the biliary tree during 5 minutes of the procedure. In all cases, the guide wire (Wilson-Cook 0.025 mm or 0.035mm in diameter) technique was used. The CBD diameter was measured at 2 cm from the papilla of Vater on radiographs taken during ERCP.

PEP was defined as serum amylase levels three times the normal with coexisting pancreatic pain 24 hours after the procedure. The inclusion criterion was therapeutic ERCP in a patient with naïve papilla of Vater, and the exclusion criteria were sphincterotomy and acute pancreatitis before ERCP. Newly analyzed risk factors were associated with the following: 1) The level of biliary stenosis-To clarify whether different anatomies (distal part, papilla level, middle part, liver hilum, multilevel, stricture pro diagnosis) resulting from different levels of stenosis have an impact on PEP risk, 2) Vater's papilla anatomy-To check if different mutual positions of the bile and pancreatic duct orifices (flat papilla, protruded papilla, papillae in the diverticulum, tumor of the papilla) alter the risk of PEP, 3) Bleeding during ES-To check whether the transverse vessel located near the upper edge of the intramural part of the papilla would alter the risk of PEP, 4) Endoscopic treatment of post-sphincterotomy bleeding-To assess whether endoscopic injection or clipping impairs pancreatic juice outflow, 5) Pathological examination conducted on the papilla-To assess whether performing multiple biopsies may cause pancreatic outlet edema, and 6) Diameter of the stent, as big as 7 Fr, introduced in the CBD-To determine whether a larger diameter of the prosthesis can increase the pressure on the orifice of the pancreatic duct. The 13 most frequently studied risk factors associated with 1) General preoperative conditions (age, sex, comorbidities), 2) Preoperative local conditions (lack of stones in CBD, normal bilirubin levels, chronic pancreatitis, sphincter of Oddi dysfunction (SOD), CBD diameter <9 mm at the level of 2 cm from the papilla, intrapancreatic CBD diameter <5 mm), 3) Procedure-associated factors (difficulty in cannulation, unintentional introduction of the guide wire into the duct of Wirsung, injection of contrast into the duct of Wirsung and pre-cut incision) were also re-analyzed.

Statistical analysis

Univariate and multivariate logistic regression analyses were used to assess the importance of the variables. The measure of risk factors was expressed as Odds Ratio (OR) with 95% confidence intervals. P values <0.05 were considered significant, and the statistical analyses were performed using MedCalc ver. 12.3 (MedCalc Software, Mariakerke, Belgium).

Results

Overall, 402 patients were enrolled in the study. Women accounted for 58.2% (234) of the study population. The average age was 66.1 years (SD 16, range 19.1-96.9); 54% (215) of the patients had comorbidities, including 43.9% (175) with cancer 16.8% (67) liver disease, 20.4% (81) cardiovascular disease, 10.3% (41) pancreatic disease, 8.5% (34) diabetes, 6.8% (27) kidney disease, 4.3% (17) central nervous system disorders, and 14% (56) other diseases. Altogether, 27 risk factors evaluated in the study group occurred with the following frequencies: biliary stenosis - in the distal part 4.48% (18), papilla level 16.8% (68), middle part 4.2% (17), liver hilum 5.5% (22), multilevel 4.2% (18), stricture pro diagnosis 24.2% (98); Vater's papilla anatomy: flat papilla 42.5% (171), protruded papilla 30.3%

(122), papilla in the diverticulum 19.4% (78); tumor of the papilla 8.2% (33); bleeding during ES 13.2% (56); endoscopic treatment of post-sphincterotomy bleeding 10.9% (44); biopsy of the papilla for pathological examination 10.2% (41); stent diameter introduced to the CBD <7 Fr 76.5% (306); age <40.8% (32); female sex 58.2% (234); systemic diseases 54.8% (218); CBD without stones 43.30% (174); normal bilirubin level 17.20 (68); chronic pancreatitis 1.5% (6); SOD 25.40% (102); CBD <9 mm 17.20% (69); intrapancreatic CBD diameter <5 mm 33.80% (136); difficulty in cannulation 46% (102); unintended guidewire introduced into the duct of Wirsung 10.70% (43); injection of contrast into the duct of Wirsung 8.2% (33); and pre-cut incision 41% (165). Based on the Atlanta classification, PEP occurred in 18 patients (4.5%), with the mild form in 10 (2.48%) patients, moderate form in 4 (1%), and severe form in another 4 (1%), including one patient (0.25%) who needed surgery. On the basis of the univariate logistic regression analysis, significant values were noted for two new risk factors, namely, flat papilla (OR 5.1, p=0.0049) and bleeding during ES (OR 3.58, p=0.148), and three already known significant risk factors, namely, age <40 years (OR 6.89, p=0.0004), CBD diameter <9 mm (OR 5.35, p=0.0007), and difficulty in cannulation (OR 3.2, p=0.0298). All these risk factors also proved to be significant in the multifactorial logistic regression analysis: flat papilla (OR 4.59, p=0.0244), bleeding during ES (OR 4.0722, p=0.0257), age <40 years (OR 4.96, p=0.0139), CBD < 9 mm (OR 3.9, p=0.0203), and difficulty in cannulation (OR 7.72, p=0.004).

Discussion

Our results suggested the existence of two new risk factors (flat papilla and bleeding during ES). They also confirmed the importance of the three previously identified factors (age <40 years, CBD diameter <9 mm, and difficult cannulation). The classification of the shape of the papilla was devised by Horiuchi and modified by Lee [10]. Furthermore, Haraldsson reported adequate repeatability for determining the shape of the papillae, even by non-experts in ERCP [11]. Our results showed that the existence of a flat papilla increased the risk of PEP by almost five-fold (OR 5.06, p=0.049). This may be due to the proximity of the pancreatic duct to the bile duct, which results in an increased probability of mechanical (failed attempts at catheterization) or thermal (during sphincterotomy) damage to the pancreatic duct orifice with consequent outflow impairment. The anatomy of the ampulla of Vater has been evaluated in only one study, in which Masci did not confirm its importance [12]. While Cheng showed that the position of the ampulla in the diverticulum reduces the risk of PEP [13], the present study did not confirm the protective effect of the presence of the diverticulum (OR= 0.2345, p=0.1619).

In summary, in the case of a flat papilla, the method of access to the CBD should be modified (e.g., two-step access). The results obtained should be confirmed in a larger group of patients using the papilla shape classification (currently used in a very small number of centers).

Bleeding during ES has not been analyzed previously. Our results showed that it increased the probability of PEP by 3.5 times (OR 3.58, p=0.0148). There are three potential explanations. First, the lack of proper visibility, which can cause manipulations close to the orifice of the duct of Wirsung. Second, its specific anatomy, where the transverse vessel runs near the top of the ampullae. Third, a technical

error involving an incision in the wrong direction (extending in the 1 o'clock direction), causing a pancreatic duct sphincter reaction [14]. This may suggest a simultaneous increase in bleeding with the risk of developing PEP. Interestingly, a higher risk of PEP was not found in patients with bleeding treated endoscopically using the injection method. This may be because, in most patients, a stent was introduced prophylactically into the duct of Wirsung to prevent impaired pancreatic outflow. This finding suggests that even the cases of self-limiting bleeding should be considered for preventive stenting.

Among the risk factors re-analyzed in the present study, age <40 years, CBD diameter <9 mm, and difficulty in cannulation were significant. All these risk factors have been well discussed [1,3,12,15,16]. The OR calculated (only in one study) for age <40 years was 1.53 [12]. In our results, this value was 6.9 and 5.6 in single and multifactorial regression analyses, respectively. CBD diameter <9 mm, based on our results, increased the risk of PEP from three times (multivariate regression) to over five times (univariate regression). Other studies analyzing a narrow CBD diameter (5-10 mm) showed an increased risk of PEP with OR values 0.8-2.6 [1,13,15]. For difficulty in cannulation, the calculated OR values in single and multifactorial logistic regression analyses were 3.2 and 7.7, respectively. In literature, the OR value ranged from 1.76 to 14.9 [1,3,15,17]. All existing differences have already been analyzed in many studies and may result from demographic differences, different sizes of analyzed groups, and the use of non-uniform definitions and criteria [1,17]. Therefore, to be able to compare the results, analyses should be conducted using uniform definitions included in the European Society of Gastrointestinal Endoscopy guidelines [1,3,7,15,17-20].

This study has some limitations. This was a retrospective single-center study; therefore, it was not possible to investigate all potential risk factors. In addition, a relatively small group of patients at a low frequency of assessed complications (4.5%) may affect the reliability of the statistical analysis.

Conclusion

Two new risk factors (flat papilla and bleeding during ES) were identified in this study. These results suggest the need for a change in ERCP methodology for managing patients with these risk factors, but this requires confirmation in subsequent studies. The study also confirmed the importance of three already known risk factors (age <40 years, difficult cannulation, and CBD diameter < 9 mm).

References

- Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated June 2014. *Endoscopy*. 2014; 46: 799-815.
- Dumonceau JM, Kapral C, Aabakken L, Papanikolaou IS, Tringali A, Vanbiervliet G, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2020; 52: 127-149.
- Testoni PA, Mariani A, Giussani A, Vailati, C, Masci E, Macarri G, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. *Am J Gastroenterol*. 2010; 105: 1753-1761.
- Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc*. 2009; 70: 80-88.
- Morales SJ, Sampath K, Gardner TB. A review of prevention of post-ERCP pancreatitis. *Gastroenterol Hepatol*. 2018; 14: 286-292.
- Zhang H, Cho J, Buxbaum J. Update on the prevention of post-ERCP pancreatitis. *Curr Treat Options Gastroenterol*. 2018; 16: 428-440.
- Lopes L, Canena J. ERCP in Portugal: a wide survey on the prevention of post-ERCP pancreatitis and papillary cannulation techniques. *GE Port J Gastroenterol*. 2018; 26: 14-23.
- DiMugno MJ, Spaete JP, Ballard DD, Wamsteker E-J, Saini, SD. Risk Models for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP): smoking and chronic liver disease are predictors of protection against PEP. *Pancreas*. 2013; 42: 996-1003.
- Miyatani H, Matsumoto S, Mashima H. Risk factors of post-endoscopic retrograde cholangiopancreatography pancreatitis in biliary type sphincter of Oddi dysfunction in Japanese patients. *J Dig Dis*. 2017; 18: 591-559.
- Lee TH, Bang BW, Park SH, Jeong S, Lee DH, Kim S-J. Precut fistulotomy for difficult biliary cannulation: is it a risky preference in relation to the experience of an endoscopist? *Dig Dis Sci*. 2011; 56: 1896-1903.
- Haraldsson E, Lundell L, Swahn F, Enochsson L, Lohr, JM, Arnelo U. Endoscopic classification of the papilla of Vater. Results of an inter- and intraobserver agreement study. *United European Gastroenterol J*. 2017; 5: 504-510.
- Masci E, Toti G, Mariani A, Curionia S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol*. 2001; 96: 417-423.
- Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol*. 2006; 101: 139-147.
- Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RCG, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc*. 1991; 37: 383-393.
- Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, et al. Risk factors for ERCP-related complications: a prospective multicenter study. *Am J Gastroenterol*. 2009; 104: 31-40.
- Dumonceau JM, Rigaux J, Kahaleh M, Gomez CM, Vandermeeren A, Deviere J. Prophylaxis of post-ERCP pancreatitis: a practice survey. *Gastrointest Endosc*. 2010; 71: 934-939.
- Testoni PA, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy*. 2016; 48: 657-683.
- Mariani A, Di Leo M, Giardullo N, Giussani A, Marini M, Buffoli F, et al. Early pre-cut sphincterotomy for difficult biliary access to reduce post-ERCP pancreatitis: a randomized trial. *Endoscopy*. 2016; 48: 530-535.
- Tse F, Yuan Y, Bukhari M, Leontiadis GI, Moayyedi P, Barkun A. Pancreatic duct guidewire placement for biliary cannulation for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. *Cochrane Database Syst Rev*. 2016; CD010571.
- Muka S, Itoi T. Selective biliary cannulation techniques for endoscopic retrograde cholangiopancreatography procedures and prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Expert Rev Gastroenterol Hepatol*. 2016; 10: 709-722.