Procedure and Patient-Related Risk Factors for Post-ERCP Pancreatitis Associated with Prophylactic Pancreatic Stent and Rectal Indomethacin

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Abstract

**Background:** Pancreatitis is one of the most crucial complications following endoscopic retrograde cholangiopancreatography (ERCP). The purpose of the current study was to investigate a potential procedure and patient-related risk factors for post-ERCP pancreatitis (PEP) in two groups: prophylactic pancreatic stent and rectal indomethacin.

**Methods:** Two different prophylactic modalities were planned and complications were assessed based on defined inclusion criteria. In this study, the patients were evaluated for the procedure and patient-related risk factors in post-ERCP pancreatitis in the recipient groups of the prophylactic pancreatic stent or rectal indomethacin.

**Results:** Pancreatitis was confirmed in 27 of all 175 selected patients after ERCP. By univariate analysis, two variables were significant with the development of PEP. Regarding the patient-related risk factors, unique subjects with common bile duct (CBD) dilated 10mm were more exposed to an increased chance of PEP (p=0.015); meanwhile, other factors didn't correlate with the increased possibility of PEP in both groups. The only procedure-related risk factor for PEP was deep cannulation of the pancreatic duct in both groups during the procedure with an incremental significant incidence of pancreatitis (p=0.005). Prophylactic pancreatic stent and rectal indomethacin showed no effects on reducing post ERCP pancreatitis. Additionally, there was no significant difference between these two strategies in the rate of PEP.

**Conclusion:** Prophylactic pancreatic duct stents and administration of rectal indomethacin cannot have particular methods for reducing the occurrence of PEP. The increase in time of deep cannulation and the presence of CBD dilation <10mm could be considered as important risk factors.

**Significance Of This Study**
What is already known?

- Post-ERCP pancreatitis (PEP) is the most important complication after Endoscopic retrograde cholangiopancreatography.
- Several risk factors for PEP including female sex, adolescent age, and history of prior PEP, SOD and absence of chronic pancreatitis.
- Several methods and medication candidates for reducing post-ERCP pancreatitis haven't been definitively proven yet.

What the new findings are?

- Our results indicated that CBD dilation < 10 mm can be considered as one important factor in increasing the risk.
- There was no significant difference in the rate of incidence of PEP among individuals with prophylactic PD stent and rectal indomethacin.

How might it impact on clinical practice in the foreseeable future?

- We need enough knowledge and best method for prophylaxis in PEP. According to our findings, sizes of CBD less than 10 mm is a risk factor of PEP and we advise to do prophylactic procedures.

Introduction

Endoscopic retrograde cholangiopancreatography is one of the most effective procedures applied in the management of pancreaticobiliary disorders [1]. The most important complications after this procedure could be post-ERCP pancreatitis (PEP), infectious problems, hemorrhage, and perforation [2–4]. One of the most common complications is acute pancreatitis that imposes critical problems like morbidity, occasional death, and increase of health care expenditures for the patients [5, 6]. The occurrence of PEP ranges from diverse studies, depending on patient selection, reported from 1-15.7%; however, this amount of high-risk cases reaches to 30% [7–9]. PEP is defined as the elevation of serum amylase and lipase of three or more times of the upper limit of normal in 24 hours with the onset or worsening pancreatic pain after the procedure. Several risk factors including female sex, adolescent age, history of prior PEP, clinical suspicion of SOD and the absence of chronic pancreatitis confirmed an effect on the increase of the occurrence of PEP [10]. Several investigations were performed to bring about solutions for the prevention of PEP; however, no method and medication for reducing post-ERCP pancreatitis has been definitively verified yet. Wire-guided biliary cannulation, placement of pancreatic duct stent and pharmacotherapy are the most principal preventive methods which have been discussed. Conflicting reports about the use of each of these methods are reported. It was confirmed that placing a stent in the pancreatic duct could play a critical role in reducing the severity of PEP in high-risk patients [11, 12]. In contrast, it is recognized that failing the placement of the stent itself can cause pancreatitis and perforation with bleeding and pain in patients [13]. Pharmacotherapy is another method which is today considered to prevent PEP, as regards, inflammatory response induced in PEP is a Physic-pathological event NSAIDs by their ability in inhibition of prostaglandins, phospholipase A2 and neutrophil endothelial interactions that can play a fundamental role in the prevention of it [14]. Some studies demonstrated that NSAIDs could reduce
complications of ERCP [15–17]. It confirmed that rectally indomethacin (100 mg) conferred protection against acute pancreatitis in high-risk patients [18]. Therefore, in the present study prophylactic stent compared with rectal indomethacin in reducing the incidence of PEP in patients.

**Methods**

Out of 620 patients referred to Taleghani hospital during one year, between Jan 2019 and Jan 2020, 175 subjects were selected to perform ERCP. All the participants provided written informed consent to participate in this study. Exclusion criteria were as follows: previous pancreatitis, interventional activities on the pancreatic duct, chronic pancreatitis, and previous failure of ERCP. ERCP was performed on patients for the following reasons: first, pancreatic cancer (n = 5), second, cholangiocarcinoma (n = 29), third, ampullary cancer (n = 6), fourth, benign strictures of the bile ducts (n = 40) fifth, Gallstone (n = 90). The provisional diagnosis of pancreatitis was applied, biliary stenting was performed in 47 subjects and a pancreatic stent was placed in 53 cases.

In the present study, unintentionally cannulation was considered as accidental entering of sphincterotomy or guidewire inside the pancreatic duct. Complete tests, including ALT, AST, bilirubin, CRP, CBC and platelet counts were performed before the procedure on selected patients. Also, the serum amylase and lipase level measured 24 h after performing ERCP again. Post ERCP pancreatitis (PEP) was defined as persistent abdominal pain following pancreatitis along with serum amylase or lipase increased 3-fold (≥ 3), 24 hours after ERCP. The increase more than three times the level of amylase in the absence of symptoms of pancreatitis in patients, 24 hours after ERCP, was considered as asymptomatic rises in serum amylase. The patients were divided between two subgroups, users of the prophylactic PD stent or rectal indomethacin.

**Statically analysis**

The chi-squared test or Fisher’s exact test was used for univariate analysis of category data, also the Student’s t-test used for the analysis of quantitative data. The level of statistical significance was considered at P < 0.05.

**Results**

175 ERCP patients (92 male and 83 female) were performed on the selected patients. The frequency of demographic and past medication history risk factors among the groups and their correlation with an incidence of PEP were shown in Table 1. Accordingly, no statically significant association was indicated between these variables and increase of incidences of PEP. The mean of quantitative research lab variables into the groups was compared with each other. (See Table 2 and Fig. 1). The analysis of the results of pre-ERCP quantitative research lab findings didn't show any significant mean difference in the patients with PEP complication and without it. Table 3 shows the frequency of intervention strategies between the groups. Overall, the interventions were performed, including placing a PD stent (n = 47),
biliary stent (n = 53), administration of rectal indomethacin (n = 128), Biliary sphincterotomy (n = 107), Balloon dilation of S.O (n = 40) and PD Guide Wire (n = 59). Guidewire biliary cannulation was achieved successfully in 89.1% (n = 156) of patients. Additionally, biliary cannulation was performed incompletely (partial) in 7.7% (n = 13) and thoroughly failed in 3.4% (n = 6). Deep cannulation was achieved in 10 minutes in 33.9% (n = 53), between 10–30 minutes in 31.4% (n = 49) and in > 30 minute in 34.6% (n = 54) of patients. In our results, there was a direct and significant relationship between the increase of the time of deep cannulation with the incidence of PEP (Table 3) (p = 0.005). The performance of cleaning biliary stone in most of the patients was successful and only failed in 17.7% (n = 31) of cases.

Evaluation of serum lipase and amylase showed the elevation of serum amylase (> 100 U/ml) and lipase (> 60 U/ml) values in 70 (40%) and 73 cases (41.7%), 24 h after ERCP, respectively. It was determined to raise threefold serum amylase in 40 (22%) patients while this increase in lipase level was found in 38 (21%) cases. The evaluation of post ERCP clinical symptoms indicated that 43 (24%) cases suffered from persistent abdominal pain. Additionally, the asymptomatic elevation of serum amylase or lipase evenly was observed in 13 subjects (7%). 3-fold increase by one of the enzymes along with abdominal pain was seen in 27 of the patients Conclusively PEP occurred in 27 (15%) cases.

Table 3 shows the frequency of ERCP findings and relationships with an incidence of PEP in subgroups received PD stent and rectal indomethacin. The investigation of the results didn't establish any association between most of the ERCP Findings variables with an incidence of PEP. It was confirmed that individuals with diameter of common bile duct (CBD) dilation 10 mm obtained a higher risk for developing PEP than the patients with the larger CBD. It was shown that the presence of small bile duct 10 mm in cases during ERCP had a significant association with increases in the incidence of PEP in patients (p = 0.015). Statistical analysis of intervention techniques didn't demonstrate a significant correlation between the variables and the incidence of PEP. There was no significant association in rates of PEP between those who received rectal indomethacin versus those who received PD stent. Notwithstanding, 21 out of 27 cases with PEP complication was among the users of rectal indomethacin.

Discussion

In this study, the role of short-term prophylactic pancreatic stents and rectal indomethacin to prevent ERCP-induced pancreatitis were investigated in patients with distinct biliary disorders. It was found that several factors increased the risk of PEP after ERCP, the extensive research in different countries was performed to know the risk factors and reduce side effects ERCP by utilizing distinct types of interventional techniques such as guide wires, consumption rectal indomethacin and placing PD stent. In a study by Cheon, Y et al. were shown that younger age (< 65 years) and female sex significantly associated with an increased risk of PEP. While this association was confirmed in other studies [19, 20], it was not supported by our results. Lack of the association between risk factors of age and sex was similarly confirmed by Cheng et al. [21]. Although the relationship between past medical variables like the history of PEP and the absence of chronic pancreatitis with post ERCP pancreatitis were estimated in some of the studies [10, 22], Our results didn't confirm such statically significant association. The
elevation of inflammatory markers 24–48 h post-procedure as a predictive factor was investigated in several studies [23, 24]. Few of the previous studies have suggested a pre-ERCP level of inflammatory markers as a potential risk factor for predicting PEP. Mohammad Alizadeh et al. established that raising pre-procedure ESR > 30 mm/hour attended a significant factor that could predict increased risk of PEP [2]. In the present study, measuring the pre-ERCP level of biochemical markers (ALT, AST, AST/ALT, CRP, WBC, and HB) didn't show any significant mean difference between two groups (patients with PEP and without it). It was found that technical strategies like biliary sphincterotomy and balloon dilation S.O could increase the risk [5, 20]. Nevertheless, our results didn't confirm a significant relationship between these variables and increase of the occurrence of PEP. Several studies have reported that wire-guided biliary cannulation is associated with a reduced incidence of PEP [25–27]. However, in agreement with the present study, this association was not established in an investigation by Mariani A. et al [28]. Notwithstanding, it did not find a correlation between the use of wired-guided biliary cannulation with increasing the risk, but our results clearly showed a direct and significant relationship between extending of the time of deep cannulation and the increased chance of pancreatitis. It seems that time-consuming and the difficulty of carrying out of this procedure can do the reduction of its performance and increased inflammation. In agreement with our results, in a study was the reported relationship between difficult cannulation and pancreatitis with Freeman ML. et al [20]. It was recognized that placing prophylactic PD stent by the increase of free flow of pancreatic exocrine secretions can due to decreasing ductal hypertension and the chance of pancreatitis, whereas the role prophylactic of PD stents in reducing the risk and symptoms of pancreatitis in patients was accepted in several studies, it was not verified by our results. The role of anti-inflammatory drugs such as diclofenac and indomethacin (100 mg) in reducing the rate of PEP has recently been considered in some of the studies [8, 14, 16], whereas the other reports have not approved this view[29, 30]. In agreement with the latter studies, our results didn't indicate the significant correlation between using rectal indomethacin and reducing PEP. In this study, the evaluation of the association between the obtained findings during ERCP and increase of incidence of post ERCP pancreatitis showed that patients with CBD dilation < 10 mm were more exposed to PEP than the other groups (See Table 4) (20 versus 7 people). Although it was no established relationship between small bile duct diameter (< 5 mm) with pancreatitis in a previous study [20], the obtained results in the present study indicated that CBD dilation < 10 mm could considerate as one important factor to increase the risk of PEP.

**Conclusion**

In this study we find that there is no statistically significant correlation between demographic and past medication risk factors with the rated PEP. Also, it did not obtain a relationship between applied interventional procedures and increase or decrease of pancreatitis. There was no significant difference in the rate of incidence of PEP among individuals with prophylactic PD stent and rectal indomethacin. It seems that small bile duct 10 mm could increase the risk of pancreatitis, so it is suggested that be avoided of the second ERCP in the patients with the small bile duct. Also, prophylactic PD stenting was performed in patients, when in performing of first CBD cannulation, the guidewire accidentally entered
inside the PD. If guidewire was not entered to PD, PD stenting was not advised because it may increase the occurrence of PEP in this patients.

Declarations

Conflict of interest:

The authors declare that they have no conflict of interest.

Ethical approval:

The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences (ethical code: IR.MUBABOL.REC.1399.371). Writing informed consent, obtained from all patients.

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Tables

Table 1
The frequency of patient-related risk factors in subgroups and relationship them with the incidence of PEP.

| variables                  | Biliary stent | PD stent | Indomethacin | Total of patients | Incidence of PEP | P value |
|----------------------------|---------------|----------|--------------|-------------------|------------------|---------|
| Female/male                | 26/27         | 26/21    | 57/71        | 83/92             | 11/16            | 0.44    |
| Smoker (yes/no)            | 7/46          | 9/38     | 15/113       | 24/151            | 1/26             | 0.449   |
| Age (<60 years/>60 years)  | 29/24         | 28/19    | 68/60        | 96/79             | 13/14            | 0.1     |
| Alcoholism (yes/no)        | 1/52          | 1/47     | 2/126        | 3/172             | 1/26             | 0.38    |
| Opium addict(yes/no)       | 2/51          | 4/43     | 5/123        | 9/166             | 1/26             | 0.7     |
| Abdominal pain (yes/no)    | 39/14         | 33/14    | 69/23        | 118/57            | 19/8             | 0.723   |
| Cholecystectomy (yes/no)   | 15/38         | 15/32    | 29/99        | 44/131            | 4/23             | 0.179   |
| History of PEP (yes/no)    | 3/50          | 4/43     | 3/125        | 7/168             | 1/26             | 0.932   |
| DM(yes/no)                 | 7/46          | 5/42     | 17/111       | 22/153            | 2/25             | 0.379   |
| Chronic-pancreatitis (yes/no) | 3/50      | 1/46     | 6/122        | 7/168             | 2/25             | 0.326   |
| Cardiopulmonary (yes/no)   | 12/41         | 8/39     | 21/107       | 29/146            | 4/23             | 0.79    |

Note: The number of patients in each group is as follows: biliary stent (n=53), PD stent (n=47), indomethacin (n=128), total of patients (n=175) and incidence of PEP (n=27) * =significant association
Table 2
The mean comparison of pre-ERCP lab findings variables between subgroups (mean ± S.E.M)

| variables   | PEP     | Without PEP | P value |
|-------------|---------|-------------|---------|
| ALT         | 108.92 ± 17 | 78 ± 6.4   | 0.195   |
| AST         | 92.3 ± 17.7  | 64.9 ± 5.1  | 0.087   |
| AST /ALT    | 1.15 ± 0.12  | 1.3 ± 0.21  | 0.64    |
| HB          | 12.3 ± 0.35   | 12.6 ± 0.75 | 0.86    |
| WBC         | 11.05 ± 2.17  | 9.9 ± 0.71  | 0.56    |
| CRP         | 16.7 ± 6.5    | 17.4 ± 2.5  | 0.91    |
| PLAT        | 251.08 ± 23.5 | 257.06 ± 9.4 | 0.83  |

Note: Incidence of PEP (n=27), individuals without PEP (n=148),* =significant association

Table 3
The relationship between applied interventional variables and the incidence of PEP in patients

| variables                  | Incidence of PEP | P value | OR     | 95%CI    |
|----------------------------|------------------|---------|--------|---------|
| Placement of stent         |                  |         |        |         |
| biliary stent              | 8(29.6%)         | 0.93    | 0.964  | 0.39–2.3|
| PD stent                   | 6(22.2%)         | 0.55    | 0.74   | 0.281–1.9|
| administration of rectal indomethacin | 21(77.8%)  | 0.55    | 1.3    | 0.5–3.5  |
| PD Guidewire               | 12(44.4%)        | 0.2     | 1.7    | 0.74–3.9 |
| Time of deep cannulation   |                  | 0.005*  | -      | -       |
| < 10 min                   | 6(22.2%)         |         |        |         |
| 10–30 min                  | 8(29.6%)         |         |        |         |
| > 30 min                   | 13(48.1%)        |         |        |         |
| Balloon dilation of S.O    | 7(25.9%)         | 0.6     | 1.2    | 0.47–3.1|
| Biliary sphincterotomy     | 16(59.3%)        | 0.82    | 0.9    | 0.39–2.1|

Note: Incidence of PEP (n=27),* =significant association
Table 4
The frequency of ERCP finding variables in subgroups and correlations these findings with incidence of PEP

| variables            | Biliary stent | PD stent | Indomethacin | Total of patients | Incidence of PEP | P value |
|----------------------|---------------|----------|--------------|-------------------|------------------|---------|
| GB dilation          | 1(1.9%)       | 1(2.1%)  | 4(3.1%)      | 5(2.9%)           | 1(3.7%)          | 0.77    |
| CBD dilation         | 33(62.3%)     | 31(66%)  | 76(59.4%)    | 107(61.1%)        | 13(48.1%)        | 0.132   |
| CBD dilation         |               |          |              |                   |                  |         |
| Diameter of CB Dilation |             |          |              |                   |                  | 0.015*  |
| < 10 mm              | 27(50.9%)     | 14(29.7%)| 66(51.5%)    | 80(45.7%)         | 20(74%)          |         |
| > 10 mm              | 25(47.2%)     | 29(61.7%)| 66(51.5%)    | 95(54.2%)         | 7(25.9%)         |         |
| CBD stricture        | 13(24.5%)     | 10(21.3%)| 37(28.9%)    | 47(26.8%)         | 11(40.7%)        | 0.07    |
| CBD stone            | 23(43.4%)     | 22(46.8%)| 58(45.3%)    | 80(45.7%)         | 4(14.8%)         |         |
| PD dilation          | 3(5.7%)       | 5(10.6%) | 5(3.9%)      | 10(5.7%)          | 1(3.7%)          | 0.62    |
| PD irregularity      | 2(3.8%)       | 3(6.4%)  | 3(2.3%)      | 6(3.4%)           | 1(3.7%)          | 0.93    |
| Malignancy           | 9(17%)        | 10(21.2%)| 30(23.4%)    | 40(22.9%)         | 8(29.6%)         | 0.36    |
| Pancreas             | 2(3.7%)       | 4(8.5%)  | 1(0.7%)      | 5(2.8%)           | 1(12.5%)         |         |
| CCA                  | 6(11.3%)      | 4(8.5%)  | 25(19.5%)    | 29(16.5%)         | 7(87.5%)         |         |
| Ampullary            | 1(1.8%)       | 2(4.2%)  | 4(3.1%)      | 6(3.4%)           | 0                |         |
| Diverticulum         | 2(3.8%)       | 0        | 8(6.3%)      | 8(4.6%)           | 0                | 0.81    |
| CBD cyst             | 1(1.9%)       | 1(2.1%)  | 1(0.8%)      | 2(1.1%)           | 0                | 0.55    |

Note: The number of patients in each group is as follows: biliary stent (n=53), PD stent (n=47), indomethacin (n=128), total of patients (n=175) and incidence of PEP (n=27), * = significant association