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Evaluation of pancreatic stent and/or suppository indomethacin efficacy in post ERCP pancreatitis prophylaxis: a single center experience

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ABSTRACT

Aim: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a serious complication of ERCP. In this study, we aimed to compare the use of rectal indomethacin, pancreatic stenting or both techniques for prevention of PEP.

Material and Method: Patients who underwent ERCP for the first time due to choledocholithiasis between January 2022 and June 2022 were retrospectively reviewed. The clinical findings, demographics, laboratory records, endoscopic intervention characteristics, whether rectal indomethacin was applied before the procedure, whether pancreatic stent was placed or not were evaluated.

Results: A total of 367 patients who underwent ERCP for the first time were included in the study. The mean age was 61 (28-92) years and 53.4% were female. In 124 (33.8%) patients, involuntary guide-wire insertion into the pancreatic duct occurred during canulation. Pancreatic stent was placed in 82 (22.3%) of the patients. Rectal indomethacin was administered to 288 patients (78.5%), while indomethacin could not be administered in 79 patients (21.5%), because they did not give consent. When patients with involuntarily pancreatic canulation were evaluated, the rate of PEP was 3.6% in the stented group, while it was 15.3% in the stent-free group (p<0001). The incidence of PEP was 20.3% in 79 patients who could not be administered rectal indomethacin, while this rate was 3.1% in those who received rectal indomethacin (p<0001).

Conclusion: The first and most important way to prevent PEP is to avoid unnecessary ERCPs. Rectal indomethacin administration reduces the risk of PEP. All patients with involuntary wires in the pancreatic duct, should be evaluated for pancreatic stent placement.

Keywords: Post-ERCP pancreatitis, rectal indomethacin, pancreatic stent, prophylaxis

INTRODUCTION

Cholelithiasis is quite common in the community and often requires hospitalization and intervention if symptomatic (1). Although the frequency of cholelithiasis varies according to geographical region and age, it can be considered as 10-30% (2-4). Choledocholithiasis is the name given to the condition that occurs when gallstones fall into the main bile duct. About 5-20% of people with gallstones develop choledocholithiasis (5-6). Endoscopic retrograde cholangiopancreatography (ERCP) is the routine treatment method used all over the world in the treatment of choledochal stones (7, 8). Although the most common indication of ERCP is choledochal stones and cholangitis, ERCP is performed with many indications such as drainage of malignant biliary obstructions, treatment of postoperative biliary complications, treatment of acute or chronic pancreatitis complications, PSC and sphincter Oddi dysfunction. ERCP is an advanced endoscopic intervention performed with a side-view endoscope, and it is mostly used for therapeutic rather than diagnostic purposes, as it has complications related to the procedure. Although ERCP is mostly considered a safe procedure, the complication rate related to ERCP has been reported between 7-12% and the mortality rate between 0.1-1.4% (9 – 12). Twenty-one studies were analyzed in a systematic review and 16885 patients were evaluated. ERCP complications were found in 7% (13). Common complications include pancreatitis, bleeding, cholangitis, and perforation.

Post ERCP pancreatitis (PEP) is a serious complication of ERCP that occurs due to mechanical or thermal damage to the pancreatic orifice, hydrostatic damage of the contrast medium, or manipulation of the guidewire. PEP is defined as abdominal pain that occurs or worsens 24 hours after ERCP with elevation of amylase or lipase to 3 times the upper limit of normal or more (14). Studies have reported the incidence of PEP between 3.5-9.7%, and the mortality due to PEP between 0.3-0.8% (13, 15).

The increase in pressure in the main pancreatic duct due to periampullary inflammation developed during canulation in the ERCP process is blamed in the development mechanism of PEP (16). Difficult canulation, guidewire entrance to the main pancreatic duct, injection of opaque material into the main pancreatic duct, balloon dilation of the biliary sphincter without EST, pancreatic sphincterotomy, and papillectomy are the conditions that increase the risk of procedure-related PEP. Conditions such as young age, female gender, history of ERCP-related pancreatitis, type 1 or 2 Oddi sphincter dysfunction can be considered among the conditions that increase the risk of PEP for the patient.

There are several strategies that can be applied to prevent the development of PEP. The most important of these is to perform the ERCP procedure with the correct indication and to avoid unnecessary procedures. Among the pharmacological prevention methods, the method accepted all over the world and recommended for routine use by the guidelines is administration of 100 mg indomethacin rectally immediately before the procedure (14, 17). In addition to indomethacin, suppository diclofenac can also be used. In addition to pharmacological techniques, there are endoscopic techniques that can be applied during ERCP. These techniques include the use of guide wire-mediated methods as the first canulation method, switching to fistulotomy or conventional pre-incision methods without persistence if conventional canulation is unsuccessful, and guide wire placement in the pancreatic duct in cases of recurrent guide wire into the pancreatic duct. In this study, it was aimed to compare the use of rectal indomethacin, pancreatic stenting or both techniques used for the avoidance of pancreatitis following ERCP.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 24.02.2022, Decision No: E1-22-2851). This study was planned as a single-center, retrospective, controlled cohort study.

Nevertheless, no patients' written informed consent was acquired because the study was retroactively planned. All procedures were performed in Ankara City Hospital, Gastroenterology Clinic. The Declaration of Helsinki's ethical guidelines and principles were followed during every procedure. Patients over 18 years of age were included in the study.

ERCP naive patients who underwent ERCP for the first time due to choledocholithiasis in our clinic between January 2022 and June 2022 were retrospectively reviewed. The electronic medical records of the patients were reviewed. The clinical findings, demographic characteristics, laboratory records, endoscopic intervention characteristics of the patients, whether rectal indomethacin was applied before the procedure, whether pancreatic stent was placed or not were evaluated. The patients were evaluated in terms of PEP 24 hours after the procedure in accordance with the guidelines.

All patients underwent the procedure after 12 hours of fasting. All patients were sedated with midazolam and/or propofol. If deemed necessary during the procedure, patients were administered 20 mg hyoscine-N-butyl bromide or 1 mg glucagon to ensure duodenal relaxation. Endoscopic procedures were performed with side-view therapeutic duodenoscopes (TJF-260V or TJF-Q180V, Olympus, Japan). In all patients, canulation was attempted with a 0.035-inch standard guidewire-loaded sphincterotome (Boston Scientific Corporation, MA, USA; Micro-Tech, Nanjing, Co, Ltd) as the first canulation method. In cases where standard canulation failed, 3 canulation methods were used depending on the papillary status or whether the guide wire was inserted into the pancreatic duct: fistulotomy, conventional precut or double guide-wire canulation. Cholangiography was taken after canulation. Afterwards, sphincterotomy was performed on the patients and the stones in the common bile duct were removed with a stone removal balloon or dormia basket.

Prophylactic pancreatic stent was placed in patients with a high risk of pancreatitis among patients who had wires to the pancreatic duct during the procedure. Prophylactic stents were removed after 3 days. Rectal indomethacin was administered to all patients who gave consent before the procedure. However, rectal indomethacin was not administered to patients who did not give consent. Ringer's lactate infusion was administered prophylactically to all patients with wire going into the pancreatic duct, at a rate of 1500cc in the first 2 hours and 1500cc in the next 8 hours.

Patients who could not be cannulated with ERCP and required PTC were excluded from the study. Patients

who underwent ERCP due to pancreatic pathologies such as chronic pancreatitis, patients who underwent drainage due to pancreatic malignancy, and patients with altered anatomy were excluded from the study. Patients who had previously undergone ERCP for any reason were excluded from the study. Only patients with proven choledocholithiasis and underwent first-time ERCP were included in the study.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to analyze the normality of the distribution of continuous variables. Continuous variables were expressed as median (interquartile range), and categorical variables were given as frequency (percentage). Continuous variables were analyzed via the Mann-Whitney U test (two groups' comparisons). Categorical variables were analyzed via the Chi-Square test or the Fisher's Exact test, followed by a post hoc test when needed. We used IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, N.Y, USA) for analyses and considered a two-tailed p-value < 0.05 as significant.

RESULTS

A total of 367 patients who underwent ERCP for the first time due to choledocholithiasis were included in the study. The mean age of the patients was 61 (28-92) and 53.4% were female. Demographic data of the patients and information about the procedure are given in **Table 1**. In 124 (33.8%) of these 367 patients, involuntary guide wire into the pancreatic duct occurred during canulation. Pancreatic stent was placed in 82 (22.3%) of these patients, who were at high risk (female gender, young age) and had wires to more than one pancreatic duct. Rectal indomethacin was administered to 288 of the patients (78.5%), while indomethacin could not be administered in 79 patients (21.5%), because they did not give consent. In 64 of the patients, both rectal indomethacin was applied and a pancreatic stent was placed.

All of the patients with pancreatic stent placed were patients with wires going into the pancreatic duct during canulation. The mean age of patients with pancreatic stent implantation was statistically significantly younger, and the majority were statistically significantly female. The incidence of PEP was 7.7% in patients without pancreatic stent placement, while this rate was 3.6% in patients with pancreatic stent placement. The difference was statistically significant (p=0.004) (**Table 2**). When patients with wires to the pancreatic duct were evaluated in terms of PEP, the rate of PEP was 3.6% in the stented group, while this rate was 15.3% in the stent-free group (p<0001).

Table 1. Basic demographic data, patient characteristics, data on the ERCP procedure	
	Total (n=367)
Age, years	61 (28-92)
Gender, female	196 (53.4)
BMI (kg/m2)	27.55 (23.51-31.51)
Comorbidity	
CAD, n (%)	48 (13.0)
COPD, n (%)	14 (3.8)
CRF, n (%)	3 (0.8)
Cholecystectomy, n (%)	126 (34.3)
Periampullary diverticulum	
Type 1	6 (1.6)
Type 2	22 (5.9)
Type 3	9 (2.5)
Type 4	5 (1.4)
Wire to the pancreatic duct, n (%)	124 (33.8)
Cannulation method	
Standard, n (%)	261 (71.1)
Conventional Precut, n (%)	14 (3.8)
Double guide-wire, n (%)	58 (15.8)
Fistulotomy, n (%)	34 (9.3)
Pancreatic stent, n (%)	82 (22.3)
Rectal indomethacin, n (%)	288 (78.5)
PEP, n (%)	25 (6.8)
Hospital stays, days	2 (2-3)
x Results are expressed as median (interquartile range) or frequency (%). BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure	

Table 2. Comparison of the group with pancreatic stent placement and the group without pancreatic stent placement				
	Total (n=367)	**No pancreatic stent placed (n=285)**	**Pancreatic stent placed (n=82)**	**P**
Age, years	61 (28-92)	68 (52-92)	47(28-68)	**0.005**
Gender, female	196 (53.4)	141 (49.4)	55 (67.0)	**0.036**
Pancreatic cannulation	124 (33.8)	42 (14.7)	82(100)	**0.001**
PEP	25 (%6.8)	22 (7.7)	3 (3.6)	**0.004**
x Results are expressed as median (interquartile range) or frequency (%). Significant P values are in bold. PEP: Post-ERCP Pancreatitis				

The incidence of PEP was found to be 20.3% in 79 of the 367 patients who could not receive rectal indomethacin because they did not give their consent, while this rate was 3.1% in those who received rectal indomethacin, and the difference was statistically significant (p<0001). On the other hand, age and gender were not statistically significantly different between the groups who received and did not receive rectal indomethacin. (**Table 3**).

Table 3. Comparison of rectal indomethacin administered and non-administered groups

	Total (n=367)	Rectal indomethacin administered (n=288)	Rectal indomethacin not administered (n=79)	P
Age, years	61 (28-92)	63 (49-92)	58 (34-74)	0.354
Gender, female	196 (53.4)	154 (53.5)	41 (51.9)	0.436
PEP	25 (6.8)	9 (3.1)	16 (20.3)	**0.001**

x Results are expressed as median (interquartile range) or frequency (%). Significant P values are in bold. PEP: Post-ERCP Pancreatitis

When all patients were evaluated, post-ERCP pancreatitis developed in 25 (6.8%) of 367 patients. The patients who developed PEP were evaluated in 4 groups according to the techniques applied for the prevention of pancreatitis as those with pancreatic stent placement, those who received rectal indomethacin, those in whom both were applied, and those who did not receive any technique. Of 25 patients who developed PEP, 14 (56.0%) were in the group that did not receive any prophylaxis. On the other hand, 8 patients (32%) were in the rectal indomethacin-only group, 2 patients were in the pancreatic stent-only group, and 1 patient was in both prophylactic group (**Table 4**).

Table 4. Distribution of patients with PEP according to prophylaxis groups

Total PEP	No PEP Protective Measures	Rectal Indomethacin Only	Pancreatic Stent Only	Rectal Indomethacin + Pancreatic Stent
25 (100)	14 (56.0)	8 (32.0)	2 (8.0)	1 (4.0)

x Results are expressed as frequency (%). PEP: Post-ERCP Pancreatitis

When all patients were evaluated, 20 of the 25 patients who had PEP had involuntary wires in the pancreatic duct. Of the 124 patients who were unintentionally inserted wires to the pancreatic duct, 82 (66.1%) had stents placed. 101 (81.5%) of these patients received rectal indomethacin; 23 (18.5%) did not. In the cross-group analyses of these patients, 71 patients received both rectal indomethacin and stenting, and only 1 (1.4%) of these individuals experienced PEP. Of the 30 patients who received rectal indomethacin without a pancreatic stent, PEP appeared in 6 (20.0%) of them. Of the 11 patients who received a pancreatic stent but no rectal indomethacin, PEP developed in 2 (18.2%) of them. Comparatively, PEP was noted in 11 (91.7%) of the 12 patients who did not have a pancreatic stent implanted or receive rectal indomethacin. A statistically significant difference was found between the groups (p<0.001).

DISCUSSION

Post ERCP pancreatitis is the most common and significant complication of ERCP, and the most important principle in its prevention is to avoid intervention in patients without a clear indication. In ERCP procedures performed with the correct indication, worldwide accepted methods for the prophylaxis of PEP are pancreatic stent placement in case of pancreatic canulation and rectal indomethacin administration to all patients before the procedure. The patients who developed PEP among the patients included in our study were mostly those who did not receive pancreatitis prophylaxis. Patients with pancreatic stenting as prophylaxis had statistically significantly lower rates of PEP than those without stenting. Similarly, PEP development was found to be statistically significantly lower in patients who received rectal indomethacin.

In a multicenter randomized study conducted by Philip et al. (18), 167 patients who had unintentional wires in the pancreatic duct were randomized, and half of them had pancreatic stent placement and half were followed without stent. While the development of PEP was 12.6% in the stented group, this rate was found to be 25% in the stent-free group. In our study, the rate of PEP was found to be 3.6% in patients who had a stent inserted in the pancreatic duct, while the rate was 15.3% in those who did not have a stent. The low rate of pancreatitis in our patients was thought to be due to the administration of rectal indomethacin to the patients. In this direction, rectal indomethacin administration to all patients at the beginning of the procedure reduces the risk of pancreatitis whether the wire goes into the pancreatic duct or not, and routine application is required.

In a systematic review of Pekgöz et al. (19), 54 articles on reducing the risk of PEP were evaluated and the importance of especially rectal indomethacin and pancreatic stenting was emphasized in the prevention of PEP development. In our study, consistent with the literature, statistical analyzes showed that pancreatic stent placement and routine administration of rectal indomethacin to all patients reduce the risk of pancreatitis in case of involuntary wire insertion into the pancreatic duct.

In a meta-analysis of 15 studies conducted by Masci et al. (20), risk factors for post-ERCP pancreatitis were evaluated, and female gender, Oddi dysfunction, and pancreatic canulation were found to be significant risk factors. In our study, the risk of PEP was found to be higher in young female patients, and these patients were treated more insistently on prophylaxis. In addition, pancreatic stenting was performed in patients with wires to the pancreatic duct, thus providing a lower rate of PEP development.

In a study by Harewood et al. (21) with 19 papillectomy patients, they placed pancreatic stent in 10 patients but did not place it in 9 patients, and found that 3 of the 3 PEPs that developed were in stentless patients. Papillectomy is a high-risk procedure for PEP, and pancreatic stenting is also effective in PEP prophylaxis in these patients. Similarly, in our study, the rate of PEP in patients with pancreatic stent insertion was found to be significantly lower than in the group without insertion.

In a study by Döbrönte et al. (22) with 228 patients, the patients were randomized, and half of the patients were administered rectal indomethacin and half were given placebo. Although the PEP rate was higher in the placebo group, it was not statistically significant. In a study by Elmunzer et al. (23) 602 patients were randomized to rectal indomethacin and placebo, and PEP developed statistically significantly less in the rectal indomethacin group. In a meta-analysis of 61 studies conducted by Yaghoobi et al. (24) it was shown that rectal indomethacin used immediately before ERCP reduced the risk of PEP in both high-risk and low-risk patients. Likewise, in our study, rectal indomethacin was found to reduce the risk of PEP for all patients.

The fact that our study was retrospective, and randomization could not be performed can be considered the weaknesses of our study. On the other hand, the fact that our center is a center with a very high volume (more than 2000 ERCPs are performed annually) prevents operator-dependent false results due to its high level of experience, constituting the strength of our study.

CONCLUSION

Post-ERCP pancreatitis is an important complication of ERCP. The first and most important way of prevention is to prevent unnecessary attempts. Rectal indomethacin administration reduces the risk of PEP in all procedures performed on ERCP naive patients with the correct indication. All patients with involuntary wires in the pancreatic duct, including all high-risk patients, should be evaluated for pancreatic stent placement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 24.02.2022, Decision No: E1-22-2851).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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