Annals of Gastroenterology (2020) **33,** 1-6

Rectal versus intramuscular diclofenac in prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: experience of a Greek tertiary referral center

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Abstract

Background Independent patient-related and procedure-related factors increase the risk of pancreatitis after endoscopic retrograde cholangiopancreatography (post-ERCP pancreatitis [PEP]). Non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated efficacy in reducing the incidence of PEP. This study investigated the difference in the incidence of PEP between intramuscular and rectal prophylactic administration of diclofenac before ERCP.

Methods We performed a retrospective analysis of data from 516 patients who underwent ERCP during the period 2014-2017. The route of diclofenac administration (rectal or intramuscular), patient-related and procedure-related risk factors, as well as serum amylase levels 18 h after the endoscopic procedure and immediate bleeding during ERCP were recorded and evaluated.

Results The overall incidence of PEP was 4.5%, without significant differences between the rectal (5.2%) and intramuscular (3.9%) routes of administration. The factor that appeared to be of significance was pre-cut sphincterotomy, since patients who underwent that procedure showed a higher probability of PEP (P=0.05; odds ratio 2.67, 95% confidence interval). Intraprocedural bleeding was almost twice as frequent in the rectal compared to the intramuscular group. Pancreatic stent placement did not appear to be statistically significant in the prevention of PEP, either alone or in combination with diclofenac administration.

Conclusions The results of our study did not reveal any statistically significant difference between the rectal or intramuscular administration of diclofenac in the prevention of PEP, contradicting the results of the majority of studies and meta-analyses published so far. One of the known risk factors associated with increased risk of PEP was also confirmed.

Keywords endoscopic retrograde cholangiopancreatography, post-ERCP pancreatitis, non-steroidal anti-inflammatory drugs

Ann Gastroenterol 2020; 33 (4): 1-6

Introduction

Pancreatitis is the most common adverse event after endoscopic retrograde cholangiopancreatography (ERCP), with an incidence of 3.5% in unselected patients [1]. Various patient-related and procedure-related risk factors have been implicated in post-ERCP pancreatitis (PEP) [1-3]. Among the drugs that have been used to prevent PEP, only non-steroidal anti-inflammatory drugs (NSAIDs: diclofenac or indomethacin) have so far demonstrated their efficiency by reducing the percentage and severity of PEP in both low- and high-risk patients [1,4-7]. The majority of previously published studies and meta-analyses support the superiority of per rectum (PR) vs. intramuscular (IM) administration of NSAIDs in the prevention of PEP [8]. Recognition of the risk factors in each patient, as well as administration of NSAIDs before or immediately after ERCP, can lead to higher success rates for the endoscopic process and lower rates of adverse events. The purpose of this study was to investigate differences in the incidence of PEP, as well as the incidence of intraprocedural hemorrhage, in patients receiving diclofenac either PR or IM prior to ERCP. A secondary aim

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Conflict of Interest: None

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Received 5 August 2019; accepted 15 November 2019; published online 10 May 2020

DOI: https://doi.org/10.20524/aog.2020.0487

was the investigation of patient-related and procedure-related risk factors for PEP manifestation, and the protective role of pancreatic stent placement.

Patients and methods

Data source and study population

The Institutional Review Board of our hospital granted permission for a retrospective collection of data from the records of patients who underwent ERCP during the 4-year period 2014-2017. Diclofenac administration (PR or IM), patient-related (female sex, previous PEP, age <50 years old, non-dilated extrahepatic bile ducts, and normal serum bilirubin) and procedure-related (duration of cannulation attempts >10 min, pancreatic guidewire passages >1, pancreatic injection, pre-cut sphincterotomy, biliary balloon sphincter dilation, and failure to clear bile duct stones) risk factors, as well as the serum amylase level 18 h after the endoscopic procedure and the immediate bleeding during ERCP, were recorded. The amylase value was assessed in all patients 18 h after the procedure (earlier or later when clinically indicated). None of the patients underwent intraductal ultrasound or pancreatic sphincterotomy. We excluded patients in whom diclofenac was contraindicated, as well as patients with missing results of serum amylase 18 h post-ERCP and those who had incomplete clinical information from the medical record or a lack of imaging studies confirming the occurrence of pancreatitis. PEP diagnosis was based on the Atlanta classification criteria, which require 2 of the following: a) abdominal pain compatible with acute pancreatitis; b) serum amylase at least 3 times above the normal limit; and c) findings of acute pancreatitis on abdominal computed tomography (CT) or other imaging method [9]. Patients with abdominal pain whose amylase value was not 3 times above the upper limit of normal (normal values: 28-100 U/L) were referred for CT scanning. Thus all patients diagnosed with PEP fulfilled at least 2 of the Atlanta diagnostic criteria. All patients were classified into 2 groups according to their indication for ERCP: choledocholithiasis or benign/malignant biliary/pancreatic stenosis.

ERCP procedure

All patients signed an informed consent form prior to endoscopic intervention. They fasted for 8 h and received 100 mg PR or 75 mg IM administration of diclofenac half to 1 h before the endoscopy. No patient received aggressive hydration after the endoscopic procedure [10,11], antibiotics or other drugs associated with the prevention of PEP [1]. Antiplatelet therapy was discontinued one week prior to ERCP, while other anticoagulants were discontinued 24-48 h before the endoscopic procedure, according to the administered regimen. All ERCPs were performed by an endoscopist experienced in biliary/pancreatic diseases, with the active involvement of trainees and in the presence of specialist nursing staff. The attempts at common bile duct cannulation were performed with the assistance of a hydrophilic guidewire, while the use of pre-cut sphincterotomy was limited to cases where cannulation was not achieved after 10 min. A pancreatic stent was placed in all patients who had pancreatic duct cannulation more than once, and in 79% of patients (41/52) with pancreatic duct injection, in order to reduce the incidence of PEP. An anesthesiologist was responsible for the administration of sedation and monitoring of the patients' vital signs during the endoscopy. Patients could consume a liquid diet 6 h after ERCP if they did not experience abdominal pain, fever or other adverse events. Vital signs, symptoms and laboratory values were monitored for at least 24 h after the procedure.

Statistical analysis

Statistical analysis was performed using SPSS Version 24. Factors associated with an increased risk for PEP were examined by univariate statistics (chi-square with continuity correction and Fisher's exact tests, as appropriate) and multivariate analyses (logistic regression method). All study variables (indication, pancreatic stent insertion, NSAID administration (PR or IM), patient-related and procedure-related risk factors) were included in the multivariate analysis. The distribution of amylase between the study groups was analyzed by Student's *t*-test. Amylase values were transformed into the natural logarithm in order to decrease the variability. Reported amylase summary was based on the geometric mean (gmean) followed by the corresponding 95% confidence interval (CI). All tests were 2-sided and statistical significance was set at $P<0.05$.

Results

During the study period (2014-2017) 688 patients underwent ERCP in our department. One hundred seventy-two patients were excluded because of a lack of information in their medical records, missing values of post-ERCP amylase, or non-administration of diclofenac (contradiction or allergy). Finally, a total of 516 patients (294 men, 222 women) of mean age 72.5 years (range 26-99) were included in the study. The indication was either choledocholithiasis (N=351, 68%) or benign/malignant biliary/pancreatic stenosis (N=165, 32%) (Fig. 1). During the 2-year period 2014-2015 all patients (N=233, 45%) received PR administration of diclofenac, whereas during 2016-2017 diclofenac was administered IM (N=283, 55%), because of availability issues in our pharmaceutical department. No patient received either PR or IM diclofenac based on any interventional study or protocol. Basic characteristics of each group, including PEP-related factors, are given in Table 1. Previous PEP, pre-cut sphincterotomy and duration of cannulation attempts >10 min were statistically more frequent in patients who received diclofenac IM, while non-dilated extrahepatic bile ducts and pancreatic injection were more frequent in the PR group. The total incidence of PEP was 4.5% (N=23), with no statistically significant differences between the PR (N=12, 5.2%) and IM (N=11, 3.9%)

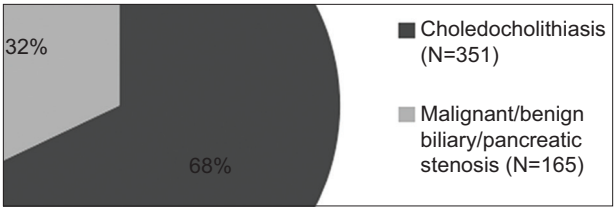

Figure 1 Indications for endoscopic retrograde cholangiopancreatography

Table 1 Basic characteristics of the patients

Characteristics	NSAID-PR N=233	NSAID-IM N=283	P-value
	n (%)	n (%)	
Indication			
Choledocholithiasis	169 (72.5)	182 (64.3)	0.058
Malignant/benign biliary/ pancreatic stenosis	64 (27.5)	101 (35.7)	
Patient related factors			
Female	102 (43.8)	120 (42.7)	0.822
Age <50 years	15 (6.5)	26 (9.2)	0.338
Normal serum bilirubin	105 (45.1)	130 (45.9)	0.913
History of pancreatitis	6 (2.6)	5 (1.8)	0.744
Previous PEP	0 (0)	14 (4.9)	**0.002**
Non-dilated extrahepatic bile ducts	66 (29.7)	58 (20.6)	**0.025**
Procedure related factors			
Failure to clear bile duct stones	30 (12.9)	30 (10.5)	0.507
Pre-cut sphincterotomy	25 (10.7)	65 (23.0)	**<0.001**
Cannulation attempts duration >10 min	55 (23.6)	94 (33.2)	**0.021**
Biliary balloon sphincter dilation	61 (26.2)	73 (25.8)	>0.999
Pancreatic injection	31 (13.3)	21 (7.4)	**0.039**
Pancreatic guidewire passages >1	13 (5.6)	24 (8.5)	0.271
Pancreatic stent placement	14 (6.0)	27 (9.5)	0.189

NSAID, non-steroid anti-inflammatory drug; PR, per rectum; IM, intramuscular; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis

routes of administration (P=0.633) (Fig. 2). In univariate analysis, regarding patient-related and procedure-related risk factors, the factor that appeared to be of statistical significance was pre-cut sphincterotomy, since patients who underwent that procedure had a 2.67 fold higher probability of PEP (P=0.05). Younger age (<50), female sex, history of pancreatitis or PEP, passage of pancreatic guidewire more than once, non-dilated extrahepatic bile ducts, pancreatic injection, normal serum bilirubin, balloon biliary sphincter dilation and failure to clear bile duct stones did

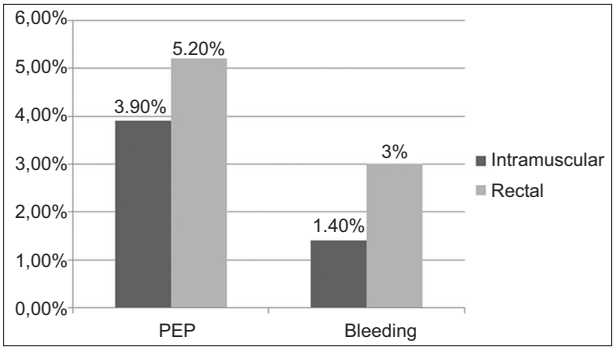

Figure 2 Association of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) and intraprocedural bleeding with intramuscular and rectal administration of diclofenac

not show any statistical significance as risk factors for PEP (Table 2). Intraprocedural bleeding (N=11, 2.1%) was almost twice as frequent in the PR (N=7, 3%) as in the IM group (N=4, 1.4%), but the difference did not reach statistical significance (Fig. 2). Most of the cases of intraprocedural bleeding (8 of 11) were treated with injection of adrenaline solution (1:10,000) while the remaining 3 were treated with the assistance of the balloon used during sphincter dilation. Pancreatic stent placement did not show any statistical significance in the prevention of PEP, either alone or in combination with diclofenac (IM or PR) administration. The gmean amylase value in PEP incidents did not show any statistically significant difference between the 2 NSAIDs subgroups (PR: 1317 U/L, 95%CI 1020-1699 vs. IM: 1179 U/L, 95%CI 741-1874; P=0.639), nor in patients who had hyperamylasemia after ERCP (PR: 230 U/L, 95%CI 198-268 vs. IM: 202 U/L, 95%CI 179-227; P=0.172), although higher gmean values were noted in the PR subgroup. In the multivariate analysis, all study variables (patient-related and procedure-related factors, indication, pancreatic stent insertion and NSAID administration) were included. Only pre-cut sphincterotomy was confirmed as a significant and independent factor for PEP (P=0.029), with these patients displaying 2.7 times greater probability of PEP manifestation (Table 2). Interestingly, between the various combinations of the above mentioned risk factors, patients who had both pre-cut sphincterotomy and failure to clear bile duct stones presented the highest incidence of PEP (30%, P=0.001).

Discussion

ERCP remains an indispensable therapeutic endoscopic procedure in the treatment of biliary and pancreatic diseases. Acute pancreatitis is one of the most common adverse events, with rates ranging from 3.5-30% in high-risk patients [1,8,11,12]. Evaluation of the patient-related and procedure-related factors associated with the occurrence of PEP, as well as the application of preventive measures (NSAIDs, pancreatic stent placement), have been widely adopted with a view to reducing the incidence of this adverse event [1,2,13]. Several pharmaceutical agents, including octreotide, somatostatin, protease inhibitors, interleukin-10, and glyceryl nitrate, have been tested for the

Table 2 Association of study variables with PEP

Variable	Presence of PEP N=23		Absence of PEP N=493		Univariate analysis		Logistic regression	
	n	%	n	%	P	OR, 95%CI	P	OR, 95%CI
Sex					0.262		0.179	
Male	10	3.4	284	96.6				
Female	13	5.9	209	94.1				
Age					0.243		0.134	
<50 years	0	0.0	41	100.0				
>50 years	23	4.9	450	95.1				
Indication					0.600		0.633	
Benign-malignant Biliary/ Pancreatic stenosis/	9	5.5	156	94.5				
Choledocholithiasis	14	4.0	337	96.0				
Pancreatic injection					0.719		0.174	
Yes	22	4.7	442	95.3				
No	1	1.9	51	98.1				
NSAID					0.633		0.259	
NSAID-PR	12	5.2	221	94.8				
NSAID-IM	11	3.9	272	96.1				
Failure to clear bile duct stones					0.328		0.467	
Yes	4	6.7	56	93.3				
No	19	4.2	437	95.8				
Normal serum bilirubin					0.398		0.359	
Increased	15	5.3	266	94.7				
Normal	8	3.4	227	96.6				
Non-dilated extrahepatic bile ducts					0.365		NA[1]	
Yes	8	6.5	116	93.5				
No	15	4.0	364	96.0				
History of pancreatitis					0.397		0.658	
Yes	1	9.1	10	90.9				
No	22	4.4	483	95.6				
Previous PEP					1		0.467	
Yes	0	0.0	14	100.0				
No	23	4.6	479	95.4				
Pre-cut sphincterotomy					**0.050**	2.67 [1.10-6.51]	**0.029**	2.70 [1.10-6.58]
Yes	8	8.9	82	91.1				
No	15	3.5	411	96.5				
Cannulation attempts duration >10 min					0.069		0.485	
Yes	11	7.4	138	92.6				
No	12	3.3	355	96.7				

(Contd...)

Table 2 (*Continued*)

Variable	Presence of PEP N=23		Absence of PEP N=493		Univariate analysis		Logistic regression	
	n	%	n	%	P	OR, 95%CI	P	OR, 95%CI
Biliary balloon sphincter dilation					0.818		0.953	
Yes	5	3.7	129	96.3				
No	18	4.7	364	95.3				
Pancreatic guidewire passages >1					0.074		0.272	
Yes	4	10.8	33	89.2				
No	19	4.0	460	96.0				
Pancreatic stent insertion					0.703		0.540	
Yes	2	4.9	39	95.1				
No	21	4.4	454	95.6				

[1]NA=Non-available: The variable "non-dilated extrahepatic bile ducts" was not included in the logistic regression because of the 13 missing values, in order to avoid reducing the number of patients entering the model

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; NSAID, non-steroid anti-inflammatory drug; PR, per rectum; IM, intramuscular; OR, odds ratio; CI, confidence interval

prevention of PEP without satisfactory results, but NSAIDs (diclofenac or indomethacin) have shown their efficacy in reducing the incidence of PEP [1,8,11,12].

In our study, the primary endpoint was any statistically significant difference between the PR and IM administration of diclofenac as regards the incidence of PEP. The meta-analyses published so far support the efficacy of PR over IM administration of diclofenac and demonstrate the efficacy of NSAIDs in the prevention of moderate to severe PEP in both average and high-risk patients [8,14,15]. However, one study demonstrated the efficacy of IM administration of diclofenac [11], while another showed no difference between PR and IM administration [16]. The present study found no statistically significant differences between PR and IM administration of NSAIDs in moderate or severe pancreatitis, or in patients with moderate or high risk. An earlier meta-analysis supported the efficacy of NSAIDs prior to ERCP [17], while more recent meta-analyses did not reveal any difference between pre- and post-ERCP administration [8,15]. All patients of our study received diclofenac before the endoscopy and we found no difference in PEP occurrence rates between the 2 subgroups (PR vs. IM).

Pancreatic stent placement contributes to the prevention of PEP [1-4,11]. In one randomized controlled trial, indomethacin was administered in addition to pancreatic stent placement in high-risk patients [18], while a meta-analysis showed that the combination of PR NSAIDs and stents is not superior to either approach alone [19]. In our study, the combination of pancreatic stent placement and diclofenac administration, either IM or PR, did not appear to lead to a further reduction in the incidence of PEP.

The rate of intraprocedural bleeding in our study was in accordance with the existing literature [2,20]. Although the rate of intraprocedural hemorrhage was twice as high in the PR compared to the IM group, this difference was not statistically significant. Differences in mean amylase values in PEP patients, as well as in those who experienced post-ERCP hyperamylasemia, between the PR and IM administration of diclofenac have not been widely investigated [16]. In our study, the mean amylase value in patients who developed PEP did not show any statistically significant difference between the 2 NSAIDs groups, nor did it differ when the analysis was limited to patients who had hyperamylasemia after ERCP.

Patient-related and procedure-related factors related to the appearance of PEP were included in the multivariate analysis. Only pre-cut sphincterotomy showed a statistically significant relation, in accordance with the existing literature [1-3,13]. The absence of statistical significance for the other risk factors can be attributed to the relatively small number of patients in our study. This parameter, along with the retrospective nature of the investigation, may represent limitations of the study.

In conclusion, administration of NSAIDs before or immediately after ERCP is supported by several meta-analyses and is a cheap, easy to administer and effective measure without major adverse events or contraindications. Numerous studies support the superiority of PR compared to IM administration of diclofenac in reducing PEP. PR administration of diclofenac is easier and less painful compared to IM administration, while there is no significant difference between them regarding cost. Although diclofenac should be administered PR in all patients, according to the results of this study, in certain cases (absence of diclofenac suppositories or patient's refusal of PR administration) the IM route could be considered.

In our study, the overall incidence of PEP was in line with previous studies, with no differences between the 2 different routes of administration (PR or IM), a result that needs further elucidation. Assessing the absolute and relative indications for therapeutic endoscopy and avoiding diagnostic ERCPs should be the first step before performing an invasive endoscopic procedure. Careful evaluation of the characteristics of patients undergoing ERCP (age, sex, history of pancreatitis or PEP, sphincter of Oddi dysfunction), as well as laboratory

measurements (serum bilirubin) and imaging (extrahepatic bile duct diameter), are essential in reducing the rate of PEP. Implementation of specific measures during the endoscopy (pancreatic stent placement, early pre-cut sphincterotomy, guidewire-assisted cannulation) further contribute in this direction. In cases of adverse events, early recognition and prompt intervention are essential to minimize prolonged hospitalization, late complications, morbidity and mortality.

Summary Box

What is already known:

- Endoscopic retrograde cholangiopancreatography (ERCP) remains an essential endoscopic procedure in the treatment of pancreatobiliary diseases
- Post-ERCP pancreatitis (PEP) is the most common and possibly serious adverse event of ERCP
- Various patient-related and procedure-related risk factors have been implicated in PEP
- Non-steroidal anti-inflammatory drugs have demonstrated their efficacy in reducing the prevalence and severity of PEP in both low- and high-risk patients

What the new findings are:

- No statistically significant differences between the rectal and intramuscular administration of diclofenac before ERCP were observed in the incidence of PEP
- Pre-cut sphincterotomy was identified as the only procedure-related factor for PEP incidence
- Intraprocedural bleeding and mean amylase values showed no statistically significant difference between the different routes of diclofenac administration

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