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Rectal diclofenac does not prevent post-ERCP pancreatitis in consecutive high-risk and low-risk patients

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ABSTRACT

Objective: rectal diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that is used to prevent pancreatitis in high-risk patients during endoscopic retrograde cholangiopancreatography (ERCP). The European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of prophylaxis with indomethacin or diclofenac in all patients undergoing ERCP, including those at low or intermediate risk of pancreatitis. A study to investigate the efficacy of this recommendation was performed.

Methods: this was a mixed cohort study. A total of 1,512 ERCP procedures performed in our institution from January 2009 to July 2016 were included in the study. Until June 2012, 718 patients did not receive diclofenac. Subsequently, 794 patients without contraindications received 100 mg of rectal diclofenac at the onset of the procedure. Risk factors for post-ERCP pancreatitis (PEAP) and PEAP cases defined using consensus criteria were recorded.

Results: a total of 47 PEAP events (3.1%) were reported, 3.4% in the diclofenac group and 2.8% in the non-diclofenac group (p = 0.554); 26.1% of patients had risk factors for PEAP. In the diclofenac group, PEAP developed in 4.4%, 0.5% and 2.6% of subjects with intact papillae, prior sphincterotomy and extended sphincterotomy, respectively. The results were similar for the non-diclofenac group: 4% with intact papillae, 0.9% with prior sphincterotomy, and 2.5% with extended sphincterotomy, respectively. PEAP severity was similar in both groups.

Conclusions: rectal diclofenac before ERCP did not prevent the development of post-ERCP acute pancreatitis in non-selected consecutive patients.

Key words: Diclofenac. NSAID. ERCP. Inflammation. Pancreas. Pancreatitis.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic technique commonly used for biliary and pancreatic conditions. The most common adverse event is post-ERCP acute pancreatitis (PEAP), which may develop in 2% to 9% of patients according to various reported series (1,2). This may represent a serious complication with significant morbidity and also mortality (3).

Patient-related factors associated with a higher potential and severity of PEAP include age below 60 years, normal serum bilirubin and sphincter of Oddi dysfunction (4,5). Technique-related factors have also been reported, including repeated and traumatic papillary cannulation, pancreatic sphincterotomy, biliary dilation without prior sphincterotomy, biliary sphincterotomy and precut (6,8). Protective factors include advanced age, malignant stricture and chronic pancreatitis (5).

PEAP development is a multifactorial process that included damage from mechanical, thermal, chemical, hydrostatic, enzymatic and microbiological causes. Therefore, several ways of reducing PEAP risk have been studied. The most promising results were obtained with the insertion of a pancreatic stent. However, stent placement may be challenging and is not exempt from complications (9,10). Various drugs have also been used to prevent PEAP from developing. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit several mediators in the inflammatory cascade that play an important

role in the pathogenesis of acute pancreatitis, primarily prostaglandins and phospholipase A-2. These drugs, when rectally administered, have been shown to reduce PEAP rates in a number of studies and meta-analyses. This beneficial effect is particularly seen in high-risk patients, including patients with sphincter of Oddi dysfunction (11-14). However, conflicting results were obtained in patients with a moderate risk for PEAP development.

A cohort study was used to assess the effect of rectal diclofenac that was administered immediately before ERCP on the incidence and severity of PEAP in consecutive patients, regardless of their risk for pancreatitis.

MATERIAL AND METHODS

The study assessed a series of patients who underwent ERCP from January 1st 2009 to July 31st 2016. It was a mixed cohort study with retrospective data collected from January 1st 2009 to May 31st 2012, and prospective data collected from May 31st 2012 until July 31st 2016. A total of 1,512 ERCP procedures were carried out. The desired duct could not be cannulated but the papilla of Vater was manipulated in 93 cases. Hence, these patients were also included in the study. ERCPs were performed by two widely experienced physicians. The study was approved by the hospital research committee. All patients signed an informed consent form.

PEAP was defined according to consensus criteria including the presence of abdominal pain consistent with pancreatitis and amylase levels at least three times the upper normal limit 24 hours after the procedure (18). PEAP severity was defined as mild (less than 3 days in hospital), moderate (four to ten days in hospital) or severe (over ten days in hospital, development of necrosis or pseudocyst) (15). All patients remained in hospital for at least 24 hours after the ERCP.

Patients were compared according to whether they received diclofenac or not. An analysis of the factors associated with PEAP development was performed. These included both patient-related (age, sex, history of recurrent acute pancreatitis, prior PEAP, chronic pancreatitis, bilirubin, choledocholithiasis and malignant stricture) and technique-related parameters (biliary sphincterotomy, pancreatic sphincterotomy, precut, Wirsung cannulation, cannulation length above ten minutes, papillary dilation

without sphincterotomy, biliary stent, Wirsung stent and sedation by anesthetist).

Statistical analysis

Data related with each patient and the exploration were collected in an Excel spreadsheet and subsequently analyzed using the IBM SPSS Statistics 20 software package. With regard to the descriptive analysis, the mean and standard deviation were used for quantitative variables and frequency distributions were used for qualitative variables. The Chi-squared test and odds ratios with their corresponding confidence intervals for categorical variables were used for the bivariate analysis. Student's t-test was used for quantitative variables with two categories and ANOVA was used for more than two categories. Finally, a binary logistic regression model was built using PEAP development as the dependent variable and factors that were significantly or almost significantly ($p < 0.1$) associated according to the bivariate analysis as independent variables.

RESULTS

A total of 1,512 patients were included; 718 did not receive diclofenac and 794 received 100 mg of diclofenac that was rectally administered at the start of the procedure. Fifty-seven patients that underwent ERCP after June 1st 2012 had a contraindication to NSAIDs and were included in the non-diclofenac group. The mean age was 73 years (SD 13.86); 818 were male (54.1%) and 694 were female (45.9%).

Table 1 shows the baseline characteristics of both groups. More patients were included in the diclofenac group and significant differences were associated with choledochal stones, Wirsung cannulation, biliary sphincterotomy, male sex and sedation by an anesthetist. More biliary stents were inserted in the non-diclofenac group.

PEAP developed in 47 patients (3.1%); 3.4% (27/47 PEAPs) of patients treated with diclofenac and 2.8% (20/47) of diclofenac-naive subjects ($p = 0.554$). In the diclofenac group, PEAP developed in 4.4%, 0.5% and 2.6% of subjects with intact papillae, prior sphincterotomy and extended sphincterotomy, respectively. Similar results were obtained in the non-diclofenac group: 4% with intact papillae, 0.9% with prior

sphincterotomy and 2.5% with extended sphincterotomy. Only six patients had a suspected sphincter of Oddi dysfunction: four in the diclofenac group and two in the control group. There was no reported PEAP in these patients.

Plastic stents were placed in the pancreatic duct of 68 patients (4.5%), 5.3% in the diclofenac group and 3.6% in the control group (p = 0.136). PEAP was mild in 78.3% of cases (37 patients). PEAP-related mortality occurred in four subjects, two in each group. PEAP severity was similar between both groups and no significant differences were found.

Table 2 shows the results of the bivariate analysis related to the influence of the various factors on the likelihood of PEAP development. No differences were found according to diclofenac administration status. A protective effect for PEAP development was reported with regard to the presence of choledocholithiasis (OR 0.43, 95% CI: 0.23-0.80) and age above 75 years (OR 0.51, 95% CI: 0.27-0.96). Wirsung stent placement had no influence (OR 1.46, 95% CI: 0.44-4.85, p = 0.52). With regard to technique-related factors, PEAP risk was increased by pancreatic duct cannulation. The risk was 3.54 fold higher (95% CI: 1.39-8.99) for guidewire cannulation and 6.05 fold higher (95% CI: 3.04-12.03) when a guidewire and contrast agent were used simultaneously. Pancreatic sphincterotomy increased the risk by a factor of 16.25 (95% CI: 1.44-182.92), cannulation longer than ten minutes increased the risk by a factor of 2.79 (95% CI: 1.55-5.02), biliary sphincterotomy increased the risk by a factor of 1.14 (95% CI: 0.47-2.75), and biliary dilation without sphincterotomy increased the risk by a factor of 31.8 (95% CI: 1.95-517.39). However, prior sphincterotomy had a protective effect with an OR of 0.19 (95% CI: 0.04-0.78). Furthermore, extended sphincterotomy had an OR of 0.69 (95% CI: 0.13-3.49) (Table 2).

According to the logistic regression analysis, the only variables that were significantly associated with PEAP were Wirsung cannulation with a guidewire, contrast or both; OR 2.77 (95% CI: 0.86-8.96), OR 3.60 (95% CI: 1.23-10.51) and OR 5.61 (95% CI: 2.39-13.18), respectively. As well as dilation without sphincterotomy (OR 401.52, 95% CI: 169.63-950.40). Age younger than 75 years increased the risk by a factor of 2.35 (95% CI: 1.14-4.83). Diclofenac was not associated with risk in our cohort (Table 3).

The cohort included a high-risk group of 394 (26.1%) patients. In this group, 183 subjects received diclofenac and 185 did not. The PEAP incidence was 8% (16 patients) in the diclofenac group and 5.1% (ten patients) in the control group. No significant differences were found between both groups (p = 0.311).

Diclofenac use did not induce more adverse effects. Eleven bleeding events were reported (1.4%) in the diclofenac group *versus* eight (1.1%) in the non-diclofenac group (p = 0.65). All bleeding events developed after sphincterotomy and no cases required admission to the Intensive Care Unit. Ten perforations occurred, 1% in the diclofenac group and 0.3% in the control group (p = 0.11).

DISCUSSION

NSAIDs were seen to be beneficial for PEAP prevention in randomized, controlled studies, as well as in several meta-analyses (11,12,16,17). Such results led the European Society of Gastrointestinal Endoscopy (ESGE) to recommend the use of indomethacin or diclofenac either before or after ERCP procedures from 2010 in their guidelines (18,19). In 2012, Elmuntzer et al. (12) reported a multicenter, randomized, controlled study that found a significant decrease in PEAP risk among high-risk patients that received rectal indomethacin after the procedure, even though over 80% of subjects had a pancreatic stent.

In this study, a similar number of PEAPs in the group treated with diclofenac (3.4%) and in the non-diclofenac group (2.8%) was found. There was in fact a tendency towards a higher number of PEAPs in the diclofenac group (27 patients *versus* 20), with an OR of 1.22 (95% CI: 0.68-2.21, p = 0.49). PEAP severity was similar in both groups. Therefore, our results differ with the above report. Thiruvengadam et al. (20) reported a retrospective study of a cohort of 4,017 patients, both high-risk and low-risk, who underwent ERCP. PEAP risk among the patients treated with indomethacin decreased by 65% (OR 0.35, 95% CI: 0.24-0.51, p < 0.001). Furthermore, PEAP severity was also lower for patients treated with indomethacin (a risk reduction of 83%). Finally, this study also found that PEAP risk had decreased by 64% in the group of patients with malignant strictures who received indomethacin. However, we found no such reduction in PEAP risk among patients with malignant strictures in our study (OR 1.14,

95% CI: 0.52-2.50).

Our results are in line with a prospective, randomized study of post-ERCP indomethacin in 449 patients by Levenick et al. (21). No drug-related efficacy with regard to the number of PEAP events was found. However, a non-significant tendency towards more PEAP episodes was found in the treated group. We cannot explain why there was a greater tendency towards pancreatitis in patients that received diclofenac. In the logistic regression analysis, we also saw that the only ERCP-related factors associated with PEAP development were pancreatic duct manipulation, whether using a guidewire, a contrast agent or both, as well as papillary dilation without sphincterotomy.

When only patients at high risk for PEAP were assessed, no differences between both groups were found. In the study by Thiruvengadam et al. (20), only 10% of patients could be included in the high-risk group. The low-risk population in this study was larger than ours. Our patient distribution was more like that of the study by Levenink et al. (21), where around 30% of patients were high-risk. Our cohort included a high-risk group of 394 (26.1%) patients. The incidence of PEAP was 8% (16/183 patients) in the diclofenac group and 5.1% (10/185 patients) in the non-diclofenac group. No significant differences were seen between both groups ($p = 0.311$) and the tendency towards more PEAP events among treated patients persisted.

A strength of our study was the fact that only two endoscopists performed all ERCP procedures in a group of non-selected, consecutive patients with no relevant differences in the technique. A weakness was the mixed cohort nature with a historic retrospective cohort as some data might have been lost, which was compared to a prospective cohort.

To conclude, rectal diclofenac before ERCP was not useful to decrease the number and severity of pancreatitis events in our patient population, which included both low-risk and high-risk subjects.

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Table 1. Baseline characteristics of patients who received rectal diclofenac as compared to patients who did not

	No diclofenac (n = 718)	Diclofenac (n = 794)	p
Patient characteristics			
Mean age	73.1 ± 14.23	72.9 ± 13.7	0.296
Older than 75 yrs	383 (53.4)	405 (51)	0.374
Older than 40 yrs	689 (96)	773 (97.3)	0.192
Males	370 (51.6)	447 (56.3)	0.071
Females	348 (48.4)	347 (43.7)	0.071
Total bilirubin (mg/dl)	6.7 ± 5.1	4.5 ± 5.2	0.292
Direct bilirubin (mg/dl)	9.2 ± 8.6	5.1 ± 5.0	0.319
Recurrent AP history	40 (5.6)	31 (4)	0.184
Prior PEAP	7 (1)	7 (0.9)	1
Chronic pancreatitis	9 (1.3)	10 (1.3)	1
ERCP indication:			
Choledocholithiasis	381 (53.1)	466 (58.7)	0.019
Stricture	165 (23)	174 (22)	0.720
Malignant	123 (17.1)	135 (17.1)	
Suspected SO dysfunction	2 (0.3)	4 (0.5)	0.689
ERCP characteristics			
Cannulation duration > 10 min	174 (24.2)	176 (22.2)	0.359
Precut	17 (2.4)	24 (3)	0.526
Biliary sphincterotomy:			
Naïve papilla	379 (52.8)	482 (60.7)	
Prior sphincterotomy	216 (30.1)	195 (24.5)	0.021
Extended	40 (5.6)	38 (4.8)	

sphincterotomy			
Wirsung cannulation With guidewire With contrast With guidewire and contrast	147 (20.5) 33 (4.6) 45 (6.3) 70 (9.7)	213 (26.8) 64 (8.1) 67 (8.5) 79 (10)	0.010
Pancreatic sphincterotomy	1 (0.1)	2 (0.3)	0.609
Dilation without sphincterotomy	1 (0.1)	2 (0.2)	1
Wirsung stent	26 (3.6)	42 (5.3)	0.136
Biliary stent	311 (43.3)	291 (36.7)	0.011
Anesthetic sedation	29 (4)	422 (53.1)	0.000

AP: acute pancreatitis; PEAP: post-ERCP acute pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography. Data are expressed as n (%).

Table 2. Results of the bivariate analysis that relate the influence of various factors to the likelihood of developing post-ERCP acute pancreatitis (PEAP)

	Post-ERCP	Pancreatitis (%)	p	OR (95% CI)
	Yes	No		
Patient characteristics				
Mean age*	67.1 ± 15.8	73.6 ± 13.8	0.002	
Age > 40 yrs	88.6	96.9	0.002	0.24 (0.09-0.66)
Age > 75 yrs	36.4	52.7	0.030	0.51 (0.27-0.96)
Males	48.9	54.2	0.47	0.81 (0.45-1.44)
Total bilirubin (mg/dl)*	3.4 ± 4.9	5.7 ± 3.8	0.689	
Direct bilirubin (mg/dl)*	4.5 ± 5.1	7.4 ± 6.4	0.082	
Recurrent AP	4.2	4.8	0.86	0.88 (0.21-3.71)
History of PEAP	1.0	0.0	1.0	
Chronic pancreatitis	2.1	1.2	0.58	1.74 (0.22-13.3)
Choledocholithiasis	39.5	60.3	0.006	0.43 (0.23-0.80)
One or two stones	25.5	34.5	0.016	0.50 (0.24-0.99)
Size > 10 mm	11.6	23.6	0.027	0.37 (0,36-0.38)
Malignant stricture	18.6	17.0	0.857	1.14 (0.52-2.50)
Rectal diclofenac	*57.4*	*52.4*	*0.49*	*1.22 (0.68-2.21)*
ERCP characteristics				
Cannulation duration > 10 min	44.7	22.4	0.000	2.79 (1.55-5.02)
Precut	2.1	2.7	0.82	0.70 (0.10-5.90)
Biliary sphincterotomy	87.2	84.3	0.010	1
Naïve papilla	76.6	56.3		1.14 (0.47-2.75)
Prior sphincterotomy	6.4	27.8		0.19 (0.04-0.78)

Extended sphincterotomy	4.3	5.2		0.69 (0.13-3.49)
Wirsung cannulation With guidewire With contrast With guidewire and contrast	55.3 12.8 10.6 31.9	22.7 6.2 7.3 9.1	0.000	1 3.54 (1.39-8.99) 2.51 (0.92-6.79) 6.05 (3.04-12.03)
Pancreatic sphincterotomy	2.4	0.1	0.002	16.25 (1.44-182.9)
Dilation without sphincterotomy	2.3	0.07	0.007	31.8 (1.95-517.39)
Wirsung stent	6.3	4.4	0.52	1.46 (0.44-4.85)
Biliary stent	43.2	39.7	0.64	1.15 (0.63-2.12)
Anesthetic sedation	34.0	29.6	0.52	1.22 (0.66-2.25)

AP: acute pancreatitis; PEAP: post-ERCP acute pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography. *mean ± standard deviation.

Table 3. Significant results of the logistic regression analysis with patient and ERCP related variables that potentially represent confounders for the development of post-ERCP pancreatitis

	p	*OR (95% IC)*
Age < 75 years	0.020	2.35 (1.14-4.83)
Wirsung cannulation	0.000	
With guidewire	0.087	2.77 (0.86-8.96)
No guidewire	0.019	3.60 (1.23-10.51)
With guidewire and contrast	0.000	5.61 (2.39-13.18)
Dilation without sphincterotomy	0.000	401 (169.63-950.40)

ERCP: endoscopic retrograde cholangiopancreatography.