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Effectiveness of rectal indomethacin in the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography in unselected patients

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ABSTRACT

Background and aims: several studies have shown that rectal indomethacin decreases the risk of acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). However, in recent studies, its effectiveness is being questioned, especially in average risk patients. Our principal aim was to evaluate the efficacy of rectal indomethacin prophylaxis in the development of post-ERCP pancreatitis (PEP).

Methods: a retrospective cohort study was conducted at a third-level university hospital. Data was collected from every patients who underwent ERCP between January 2014 and June 2016. After February 2015, all patients received 100 mg of rectal indomethacin prior to ERCP. We analyzed groups, with indomethacin and without indomethacin, in unselected patients.

Results: a total of 524 patients were analyzed, with a mean age of 71.1 ± 17.0 (standard deviation [SD]) years. Of the total number of patients, 393 (75%) had an average risk; 277 received rectal indomethacin prior to ERCP, while 247 did not. In the group with indomethacin, 12 patients developed PEP (4.33%) *versus* ten in the indomethacin-free group (4.04%) (OR 1.33; 95% confidence interval [CI], 0.52-3.40; p = 0.56). Severe-moderate PEP

developed in seven patients (2.52%) in the indomethacin group and in two patients (0.81%) in the indomethacin-free group (p = 0.24). Previous sphincterotomy was a protective factor (OR 0.02; 95% CI, 0.02-0.2; p = 0.001) and age < 45 years was a risk factor: (OR 3.43; 95% CI, 1.14-10.32; p = 0.03).

Conclusions: rectal indomethacin does not appear to decrease the risk of developing PEP in unselected patients.

Keywords: Rectal indomethacin. Pancreatitis. Prevention. Endoscopic retrograde cholangiopancreatography.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an important therapeutic tool for pancreatobiliary diseases. Acute pancreatitis is the most frequent and feared post-procedural complication following ERCP, with an incidence between 1.6% and 15%, although in most studies it is between 3-5% (1,2). Post-ERCP pancreatitis (PEP) is often mild (approximately 80%), but when it is severe, it accounts for substantial morbidity and mortality (3).

Several patient-related risk factors have been identified for PEP, including young age, female sex, Oddi' sphincter dysfunction, prior PEP and history of acute recurrent pancreatitis (≥ 2 episodes). Procedure-related risk factors include: difficult cannulation, pancreatic duct injection, pancreatic sphincterotomy, endoscopic papillary large-balloon dilation of an intact sphincter, precut sphincterotomy and endoscopy papillectomy (4-7).

A number of measures have been studied in an effort to reduce the incidence of PEP, like different endoscopic techniques and drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to regulate proinflammatory mediators in acute pancreatitis (AP) by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet activating factors. These have been proven to decrease the incidence of PEP in many studies, although a small number of these are prospective studies. Most existing prospective studies evaluate high-risk patients (8-11). As a result of this studies, the European Society of Gastrointestinal Endoscopy in 2014 and the American Society for Gastrointestinal Endoscopy in 2017 recommended routine rectal administration of 100 mg indomethacin or diclofenac during

ERCP in all patients without contraindication (7,12). However, recent studies have reported contradictory results. Some studies did not find effectiveness of NSAIDs in average risk (13-16). Similar to the results of these studies, in the last few years, several meta-analyses have been published with similar contradictory results (17-23). This study was conducted to determine the benefit of rectal indomethacin in preventing PEP in unselected patients.

MATERIALS AND METHODS

A retrospective cohort study was conducted at a third-level university hospital. Our data was collected from all patients (older than 18 years) that underwent ERCP between January 2014 and June 2016. After February 2015, all patients received 100 mg of rectal indomethacin prior to ERCP; no one received indomethacin before this period because the hospital did not have rectal indomethacin available until that date. Patients admitted with a diagnosis of AP were excluded.

Data on demographic and clinical features, procedures characteristics, development of PEP and adverse events after the procedure were collected from patients' records. An analysis by groups was made: patients with indomethacin and without indomethacin. Patients who had at least one major and/or two minor risk factors for developing post-ERCP pancreatitis were defined as high-risk patients. According to the reviewed literature, major risk factors were considered as follows: history of previous PEP, Oddi's sphincter dysfunction (type III), difficult cannulation (> 10 attempts), pre-cut sphincterotomy, pancreatic sphincterotomy. The minor risk factors considered were: female sex, younger age (≤ 45 years) and contrast injection in the pancreatic duct (3,5-7). Patients were considered to have an average risk for pancreatitis if they did not meet the criteria for high risk.

The primary study outcome was whether 100 mg of rectal indomethacin, compared to no indomethacin, would decrease the rate of AP in general patients (unselected patients) undergoing ERCP. PEP was defined according to consensus criteria including the presence of abdominal pain consistent with pancreatitis and amylase levels at least three times higher than the upper normal limit, more than 24 hours after procedure (24). The patients remained hospitalized for at least 24 hours after the ERCP. The secondary outcomes were: assessing the severity of PEP in those receiving indomethacin *vs* without indomethacin and determining which risk factors were related to the development of PEP. The severity of

pancreatitis was defined by the Cotton criteria and/or the revised Atlanta classification: mild required 2-3 days of hospitalization and/or no organ dysfunction; moderate required 4-10 days of hospitalization and/or transient organ failure < 48 hours; and severe adverse events required more than ten days of hospitalization and/ or persistent single or multi-organ failure > 48 hours.

The analysis was carried out with the SPSS program version 22. The Student's t test was used for the quantitative variables and the Chi-squared test, for categorical variables. An analysis of possible factors associated with PEP was conducted by performing univariate logistic regression analysis with PEP development as the dependent variable and the following independent variables: younger age (≤ 45 years), female sex, rectal indomethacin, prior to PEP, previous sphincterotomy, procedure indication (acute cholangitis, choledocholithiasis, malignant biliary obstruction, replacement of biliary stent, benign biliary stricture and failed ERCP), procedural factors (precut sphincterotomy, biliary sphincterotomy, difficult cannulation, pancreatic duct injection, pancreatic sphincterotomy, balloon dilation of an intact biliary sphincter, wire cannulation of pancreatic duct, double guide, pancreatic stent placement and biliary stent placement). Any variable associated with PEP ($p < 0.15$) in the univariate analysis was included in multivariate binary logistic regression model with PEP as the dependent variable. In addition, possible interactions and/or confounding factors were evaluated, including the following potential confounding factors: malignant biliary obstruction, biliary sphincterotomy, balloon dilation of an intact biliary sphincter and double guide. They were also included in the final logistic regression model.

Another secondary propensity score adjustment analysis was performed comparing the indomethacin group *vs* without indomethacin group. The logistic regression model used to derive the propensity score included the following 20 variables: age < 45 years, sex (female), comorbidities, previous PEP, pancreatic stenosis, acute cholangitis, choledocholitiasis, malignant biliary obstruction, replacement of biliary stent, benign biliary stricture, failed ERCP, previous sphincterotomy, biliary sphincterotomy, double guide, balloon dilation of biliary sphincter, difficult cannulation of pancreatic duct, pancreatic stent placement, biliary stent placement, pancreatography and wire cannulation of pancreatic duct.

RESULTS

A total of 524 patients were included and analyzed, with a mean age of 71.1 ± 17.0 (SD) years; 238 were male (45.4%). Our sample had 393 average risk patients (75%). Two hundred and seventy-seven (52.9%) received rectal indomethacin prior to ERCP (indomethacin group), while the remaining 247 (47.1%) did not receive prophylaxis (without indomethacin group). There were 159 (57.4%) females in the indomethacin group and 127 (51.4%) in the control group (p = 0.17). The mean age of the patients in the indomethacin group was 71.4 ± 16.3 years, and in the without indomethacin group it was 70.8 ± 17.8 years (p = 0.7). Table 1 summarizes the rest of the baseline characteristics of both groups. Both groups were quite similar, the only differences being rates of indication for choledocholithiasis and benign biliary stricture. These variables were not confounding factors in the multivariate regression analysis. Regarding the procedure characteristics, no significant differences were found between groups with and without indomethacin in: failed ERCP; number of stent placement (pancreatic stent); difficult cannulation; pancreatic sphincterotomy; precut sphincterotomy and other sphincter manipulation (Table 2). Significant differences were found in the percentage of pancreatography in both groups, being higher in the group without indomethacin (without indomethacin 13.8% *vs* with indomethacin 4%, p < 0.01). However, it was not a confounding factor in the multivariate regression analysis.

In the group with indomethacin 12 patients developed PEP (4.33%) compared with ten in the indomethacin-free group (4.04%) (OR 1.07; 95% CI, 0.45-2.52; p = 0.87) (Fig. 1). The multivariable analysis did not show that indomethacin was a protective factor in developing PEP (OR 1.32; 95% CI, 0.5-3.4; p = 0.56) (Table 3). With the secondary propensity score adjustment analysis, rectal indomethacin had an adjusted OR of 1.07 (95% CI, 0.42-2.74; p = 0.8), thereby confirming the findings from the primary multivariable model.

Severe-moderate PEP developed in seven patients in the indomethacin group (2.52%) and in two patients in the group without indomethacin (0.81%) (p = 0.24). Mild PEP developed in five patients in the indomethacin group (1.81%) and in eight from the group without indomethacin (3.23%) (p = 0.69) (Fig. 1). No statistically significant differences were found in the rates of gastrointestinal bleeding and hospital stay (p = 0.7 and p = 0.93, respectively) (Fig. 1).

Factors associated with the development of PEP were subsequently studied, finding that the previous sphincterotomy was a protective factor (OR 0.02; 95% CI, 0.02-0.2; p = 0.001) and that age under 45 was a risk factor (OR 3.43; 95% CI, 1.14-10.32; p = 0.03). No statistically significant differences were found in the rest of analyzed factors (Table 3).

DISCUSSION

Our findings showed that a 100 mg dose of rectal indomethacin given before ERCP in unselected patients does not prevent PEP. In addition, there was no significant difference in the proportion of patients with mild, moderate and severe PEP in both groups. These results are similar to those of some recently published studies by Levenick et al. and Döbrönte et al., focusing on population with average risk (70% in Levenick et al.). Conversely, Elmunzer et al., Andrade-Davila et al. and Patai et al. (9,10,25) mainly evaluated high-risk population (82% suspicion of Oddi's sphincter dysfunction in Elmunzer et al., 100% with high-risk in Andrade-Davila et al. and 72.9% with high-risk in Patai et al.). Our population had, in their majority, an average risk (75%) and were not excluded by indication or intervention, being these the most frequently found patients in general practice. The overall rate of PEP in our study was 4.2%, which was lower than the mean rate of pancreatitis in previous studies of high-risk patients in NSAID pharmacoprophylactic studies.

Similar to these randomized controlled trials (RCT), different meta-analyses have been published with contradictory results. Patai et al. and Yang et al. (20,21) conclude that NSAIDs are effective in reducing the incidence of PEP in high- and average-risk patients. These included 17 and 12 studies respectively and only eight of them evaluated the use of rectal indomethacin (8-10,13-15,25,26). Three of these eight studies (Elmulzer et al. [9], Andrade-Davila et al. [10] and Patai et al. [25]) studied high-risk population, concluding that, in this population, rectal indomethacin significantly reduced PEP. The rest of these eight studies evaluated unselected or average risk population, obtaining different results. Döbrönte et al. in 2012 and 2014 and Levenick et al. (13-15) did not find that rectal indomethacin decreased the incidence of PEP in unselected or average population. Sotoudehmanesh et al. (8) assessed unselected population but only found effectiveness of rectal indomethacin in high-risk population (post-hoc subgroup analysis). Finally, Montaño et al. (26) included a population with suspected biliary obstruction without clearly specifying if the population had

high- or average-risk, but recommending the use of indomethacin, especially in patients with risk factors. In summary, in these eight studies, which analyze the effectiveness of rectal indomethacin, it can be seen that there is more conclusive evidence regarding the effectiveness of rectal indomethacin in high-risk population than in average-risk population. This was demonstrated by Indamar and Wan meta-analysis, which included these eight RCT, finding effectiveness of rectal indomethacin in high-risk population but not in average-risk patients (17,18). These meta-analyses are in concordance with our results, because we did not find effectiveness for rectal indomethacin to prevent PEP in unselected population that had in their majority an average risk. However, they are contrary to those of a recent multicenter, single-blinded, randomized controlled trial (11), where a decrease in the frequency of PEP in average-risk population with indomethacin was found as compared with those without indomethacin (3% *vs* 6%, OR 0.46; 95% CI, 0.3-0.71; $p < 0.05$).

Some RCT have shown that prophylactic placement of a pancreatic duct stent in high-risk patients reduces the incidence of pancreatitis by mechanically facilitating pancreatic duct drainage (27,28). Many previously described studies did not exclude the use of pancreatic stent, which may influence the results. There are few studies considering this, trying not to include patients who had a pancreatic stent or minimizing its use (15). In our study, the use of pancreatic stent was similar in both groups, with (2.5%) and without indomethacin (2.8%) ($p = 0.82$), and it was only used in a few cases.

In the multivariable analysis of risk factors for the development of PEP, age under 45 years turned out to be an independent risk factor (OR 3.43; 95% CI, 1.14-10.32; $p = 0.03$). This result is similar to those of previous reports (4-7). The reason for the higher rate in young patients may be attributed to the increased pancreatic secretion function in young and middle-aged people compared to older people (29). On the other hand, previous sphincterotomy proved to be a protective factor to develop PEP (OR 0.02; 95% CI, 0.02-0.2; $p = 0.001$). This protective factor had not been described so far. In our opinion, this is due to the fact that many of these studies included patients with native papilla in its majority (30,31). In our case, 39% of patients with previous sphincterotomy were included. Due to this larger number of patients, it might have been possible to see in the multivariable analysis that sphincterotomy was an independent protective factor for the development of PEP. This would also explain the low PEP rate in our series.

In conclusion, our study suggest that rectal indomethacin is not useful for unselected patients. One of the limitations of the present study is its being a retrospective cohort study. More studies are needed, especially in average-risk population, because it remains unclear whether the prophylactic use of rectal NSAIDs in unselected patient is a better strategy than their administration in high-risk patients only.

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Patients characteristics	*Indomethacin group* (n = 277)	*Without indomethacin group* (n = 247)	*p value*
Age (media ± SD)	71.4 (± 16.3)	70.8 (± 17.8)	0.70
Gender female (%)	159 (57.4)	127 (51.4)	0.17
Comorbidities (CIRS ± SD)	6.33 (± 3.6)	6.22 (± 3.9)	0.74
Hospital stay (days)	9.91 (± 9.2)	9.84 (± 10.3)	0.94
CPRE indication, n (%)			
Acute cholangitis	76 (27.4)	51 (20.6)	0.70
Choledocholithiasis	*93 (33.6)*	*111 (44.9)*	*0.01*
Malignant biliary obstruction	44 (15.9)	25 (10.1)	0.51
Replacement of biliary stent	28 (10.1)	29 (11.7)	0.54
Biliary fistula	5 (1.8)	2 (0.8)	0.54
Benign biliary stricture	*11 (4.0)*	*23 (9.3)*	*0.01*
Pancreatic stenosis	3 (1.1)	1 (0.4)	0.59
Ampulectomy	5 (1.8)	3 (1.2)	0.84
Others	12(4.3)	2 (2.4)	0.01
Previous sphincterotomy, n (%)	109 (39.4)	98 (39.7)	0.93
Previous PEP	5 (1.8)	8 (3.2)	0.29

*CIRS: Cumulative Illness Rating Scale

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Table 1. Baseline characteristics of patients who received indomethacin *vs* without indomethacin

SD: standard deviation; CPRE: endoscopic retrograde cholangiopancreatography; PEP: post-ERCP pancreatitis.

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Table 2. Characteristics of the procedure

Procedural characteristics	*Indomethacin group* (n = 277)	*Without indomethacin group* (n = 247)	*p value*
Sphincter manipulation, n (%)			
Precut sphincterotomy	3 (1.1)	2 (0.8)	0.74
Biliary sphincterotomy	144 (52)	124 (50.2)	0.68
Pancreatic sphincterotomy	2 (0.7)	4 (1.6)	0.58
Balloon dilatation of biliary sphincter	4 (1.4)	13 (5.3)	0.14
Double guide	10 (3.6)	8 (3.2)	0.82
Difficult cannulation (10 attempts)	8 (2.9)	5 (2.0)	0.53
No	106 (38.3)	91 (36.8)	
Pancreatic duct manipulation, n (%)			
Pancreatography	*11 (4.0)*	*34 (13.8)*	*< 0.01*
Wire cannulation of pancreatic duct	14 (5.1)	11 (4.5)	0.74
No	252 (91)	202 (88.8)	
Stent placement, n (%)			
Biliary stent placement	73 (26.4)	56 (22.7)	0.32
Pancreatic stent placement	7 (2.5)	7 (2.8)	0.82
Biliary and pancreatic stent placement	2 (0.7)	2 (0.8)	1.00
Other interventions	1 (0.4)	0 (0.0)	1.00
No	194 (70)	182 (73.7)	
ERCP failed, n (%)	8 (2.9)	13 (5.2)	0.16

Table 3. Multivariable logistic regression analysis of risk factors for PEP

	p value	*OR*	*CI (95%)*
Age younger than 45 years	*0.03*	*3.43*	*1.14-10.32*
Acute cholangitis	0.08	0.21	0.04-1.22
Choledocholithiasis	0.51	0.69	0.22-2.12
Malignant biliary obstruction	0.05	0.11	0.01-1.03
Previous sphincterotomy	*0.001*	*0.02*	*0.002-0.21*
Pancreatography	0.39	1.76	0.49-6.38
Pancreatic cannulation	0.89	1.14	0.18-7.37
Rectal indomethacin	0.56	1.33	0.52-3.40
Double guide	0.44	0.46	0.06-3.33
Wire cannulation of pancreatic	0.89	1.13	0.17-7.37
Balloon dilatation of biliary sphincter	0.71	1.65	0.11-24.76

OR: odds ratio; CI: confidence interval.

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Fig. 1. Twelve patients of 277 (4.3%) developed post-ERCP pancreatitis (PEP) in the indomethacin group and ten of 247 patients (4.0%) in the without indomethacin group (p = 0.87). Seven patients developed moderate-severe PEP in the indomethacin group (2.5%) *vs* two patients in the without indomethacin group (0.8%) (p = 0.24). Five patients developed mild PEP in the indomethacin group (1.8%) *vs* eight patients in the without indomethacin group (3.2%) (p = 0.69). Four patients developed gastrointestinal bleeding in the indomethacin group (1.4%) *vs* ten patients in the without indomethacin group (4%) (p = 0.7). Fifteen patients presented more than 30 days hospital stay in the indomethacin group (5.4%) *vs* 13 in the without indomethacin group (5.3%) (p = 0.93).