



## Intramuscular Diclofenac as Prophylaxis for Post ERCP Pancreatitis

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### Abstract

**Background:** Post-ERCP pancreatitis (PEP) is one of the potentially serious complications of this procedure; in general population it occurs in approximately 1% to 10% of patients, but most cases are mild or moderate. Several studies have demonstrated the safety and efficacy of NSAIDs in the prevention of PEP. However, most of these trials have used the rectal route and it is not clear whether the parenteral route of administration is as effective as the rectal route.

**Objectives:** To determine if there is a difference between the events of acute pancreatitis in patients undergoing ERCP with the use of diclofenac 75 mg intramuscularly.

**Methodology:** We proceeded to take the data of all patients scheduled for ERCP in the Gastroenterology Unit of Hospital Roosevelt, during the months of March and April of 2019. After the procedure they were followed up for 24 hours looking for signs of acute pancreatitis. If suspected, it was confirmed, and the complication was managed.

**Results:** A total of 81 patients were included, which were randomized in the study group - 35 (diclofenac 75mg) and control group - 46 (0.9% saline). Five patients presented PPC, which is equivalent to 6.17% of the sample. Differences were found in PPC events with the use of intramuscular diclofenac, with a RR of 1,161.

**Conclusions:** The use of diclofenac 75mg IM prior to ERCP increases the risk of PPC with a RR of 1,161.

**Keywords:** ERCP; Pancreatitis; Diclofenac; NSAID

### Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is used for diagnosis and treatment of pancreatic and biliary diseases [1]. Post-ERCP pancreatitis (PEP) is one of the potentially serious complications of this procedure, with a frequency close to 30% in patients with high risk conditions such as Oddi sphincter dysfunction [2], in the general population it occurs in approximately

1% to 10% of patients, but most cases are mild or moderate [3]. PEP seems inevitable even in the hands of endoscopists experts. Consequently, interventions should be sought to reduce the rate of this complication [4]. The development of PEP is a multifactorial process that includes mechanical, thermal, chemical, hydrostatic, enzymatic and microbiological damages. For this reason, different ways to reduce the risk of PEP have been studied. The insertion

of a pancreatic prosthesis is the one that has shown the best results. However, it is not always easy to place a prosthesis and this technique is not free of complications either [5]. The risk factors that increase the risk of PEP are classified as related to the patient (young, female, suspicion of sphincter of Oddi dysfunction, recurrent pancreatitis, normal bilirubin, history of PEP, etc.), related to the procedure (multiple contrast medium injections, difficult cannulation, balloon dilation, pancreatic sphincterotomy, etc.) and related to the operator (training or experience of endoscopist) [6]. Research published results in the network have given conflicting results, where they have not found benefit from the use of NSAIDs as a preventive measure [5,7,8], however several randomized studies, as well as meta-analyses, have shown safety and efficacy of NSAIDs in the prevention of PEP [1,4]. Interestingly, however, most of these trials have used the rectal route of NSAIDs and it is not clear if the route of parenteral administration is as effective as the rectal route [2].

## Methodology

Non-observational, prospective, cross-sectional and analytical study was carried out. We proceeded to take baseline characteristic data to all patients scheduled for ERCP in Roosevelt Hospital, Gastroenterology Unit, during the months of March and April 2019, which included not only demographic information, but also indication of procedure and laboratory values. Then simple randomization between diclofenac 75mg and placebo (0.9% saline solution) intramuscularly was performed. Patient and endoscopist were blind about the prophylaxis, only researcher knew which group the subject belonged to. Then, data inherent to the endoscopic procedure were taken, such as cannulation attempts, duration of the procedure, sphincterotomy, extra procedures, among others. Patients were monitored while awaking from the respective anesthetics and medically evaluated for clinical signs of acute pancreatitis. If the initial evaluation was negative, they were discharged home or to their service bed. Hospitalized patients were given face-to-face clinical follow-up, and outpatients were called at 24 hours interrogating signs of acute pancreatitis. If at any time an outpatient participant had suspected acute pancreatitis, it was admitted to confirm and management. The diagnosis of acute pancreatitis was made according to the current guidelines (at least 2 out of 3 - characteristic abdominal pain, elevation of 3 times amylase/lipase upper normal value and cross-sectional radiographic evidence) [9]. Patients who met the following inclusion criteria were included:

over 18 years of age, scheduled for ERCP in Hospital Roosevelt, Gastroenterology Unit, and who signed informed consent. Within the exclusion criteria, patients who lost their follow-up during the following 24 hours.

## Objectives

- **Primary Objective:** To determine if there is a difference between the events of acute pancreatitis in patients undergoing ERCP with the use of diclofenac 75 mg intramuscularly.
- **Secondary Objective:** Establish the risk factors for the development of PEP.

## Statistical analysis

The statistical analysis was performed in SPSS 25. Categorical variables were presented in frequencies and percentage and analyzed with Chi Square of homogeneity and Fisher's exact test. Normality was assessed according to the Kolmogorov-Smirnov and Shapiro-Wilk statistics. Numerical variables were evaluated according to Mann-Whitney U and t-student independent samples. It is considered a statistically significant  $p$  less than 0.05.

## Results

A total of 96 patients were included, were randomized in study group - 48 (diclofenac 75mg) and control group - 48 (saline 0.9%). Fourteen and two patients in study group and placebo respectively, did not answer the phone call, so they were excluded for final evaluation. Median values for numerical variables: age 47.14 years, weight and height 63.10 kg. and 1.58 m. respectively, BMI 25.22 Kg./m<sup>2</sup>, WBC (white blood cell) 9.99 K/ul, amylase 86.12 U/l, lipase 90.36 U/l, total bilirubin 6.92 mg/dl, TGO 118.24 U/l, TGP 128.52 U/l, ALP (Alkaline phosphatase) 431.60 U/l, GGT 445.26 U/l, procedure duration 13.08 min. Categorical variables, majority of patients were from rural origin and residence, female, with choledocholithiasis as an ERCP indication, without difficult cannulation (defined as cannulation with less than 8 attempts), sphincterotomy was performed, with ballooning, placement of stent and without lithotripsy. After 24 hours of face-to-face follow-up (hospitalized patients) and by telephone (outpatients) was determined that 5 patients presented with PEP (without organic dysfunction), and 17 patients presented abdominal pain not associated with acute pancreatitis. The values of the variables broken down by study and control group are indicated in Table 1. The relative risk for presenting PEP with the use of diclofenac was 1,161 (Table 2).

		Diclofenac No. 18	Placebo No.26	p
<b>Variable</b>		<b>No.</b>	<b>No.</b>	
Residency	Urban	6	12	0.280
	Rural	12	12	
Origin	Urban	8	8	0.531
	Rural	10	16	
Gender	Masculine	6	6	0.174
Indication	Malignant Obstruction	0	2	0.221
	Benign Obstruction	0	2	
	Choledocholithiasis	14	18	
	Other	4	2	
Difficult cannulation*		6	4	0.300
Successful cannulation		18	22	0.498
Esfinterotomy		16	18	0.431
<b>Balloon extraction</b>		12	12	0.280
Endoprosthesis		4	2	0.375
Lithotripsy		2	0	0.178
Otro Procedimiento		2	0	0.178
PEP		2	0	0.178
Abdominal Pain**		4	2	0.212
		Median (SD)	Median (SD)	
Age years		44.56 (±22.56)	38.83 (±18.01)	0.366
Weight kg.		61 (±5.75)	65.18 (±18.29)	0.362
Height m.		1.54 (±0.06)	1.58 (±0.06)	0.036
BMI Kg/m <sup>2</sup>		25.86 (±3.15)	25.37 (±5.52)	0.749
WBC K/uL		11.54 (±3.48)	8.50 (±2.79)	0.005
Amylase U/l		130.65 (±82.34)	61.50 (±16.74)	0.130
Lipase U/l		162.54 (±150.79)	50.80 (±2.54)	0.174
TB mg/dl		8.64 (±10.64)	6.59 (±8.35)	0.511
TGO U/l		91.19 (±135.36)	71.96 (±34.27)	0.609
TGP U/l		117.61 (±141.58)	82.50 (±74.65)	0.408
ALP U/l		368.16 (±345.84)	366 (±224.89)	0.982
GGT U/l		363 (±417.10)	506.62 (±700.21)	0.564
Procedure duration min		18 (±9.92)	24 (±7.07)	0.361
*Difficult cannulation: greater than 8 attempts; *Abdominal Pain: Not Secondary to Acute Pancreatitis. SD: Standard Deviation; BMI: Body Mass Index; WBC: White Blood Cell, TB: Total Bilirubin; TGO: Glutamic Oxaloacetic Transaminase; TGP Pyruvic Glutamic Transaminase; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl Transpeptidase.				
Source: Data Collection				

**Table 1:** Basal Characteristics.

	Pancreatitis	No Pancreatitis	P	RR (CI) 95%
Diclofenac	5	30	0.008	1.161 (1.019-1.326)
Placebo	0	46		
CI: Confidence Interval				
Source: Data Collection.				

**Table 2:** Bivariate Analysis.

**Analysis**

Accordingly to the results previously expressed, we can observe that diclofenac administered intramuscularly showed statistically significant difference, comparing the study group vs. the placebo group in the incidence of PEP. It is noteworthy that 17 patients presented abdominal pain not associated with pancreatitis, which could be dyspepsia secondary to fasting, and in study group further exacerbated by NSAIDs, or even inherent in the instrumentation of the digestive tract. PEP events are of multicausal and multifactorial origin, in this review the incidence of pancreatitis after the procedure was 6.17%, which approximates the majority of publications in other parts of the world [2,3,5,7,8]. The 5 reported PEP events were without organic dysfunction, which also agrees with the severity reported in other publications [1,4]. The use of intramuscular diclofenac prior to ERCP was associated with an increase in PEP cases, with an incidence in its group of 14.28% compared to zero cases in control group; with a statistical difference of 0.008 and a relative risk of 1,161 (1,019 - 1,316 - 95% CI). It was planned from the protocol to collect a sample for a full year, however, observing that all PEP events were present in the study group it was decided to stop the collection. Among the other variables studied, the only ones that were statistically different with respect to the presence of PEP were bilirubin levels (p 0.006) and cannulation attempts (p 0.047). It is important to clarify that, within the limitations for this review, we have that it was in a single hospital, and that the laboratory results were not from the same center.

**Conclusion**

The use of diclofenac 75mg IM prior to ERCP increases the risk of PEP with a relative risk of 1,161. Other factors that were different between the pancreatitis and non-pancreatitis groups were the number of cannulation attempts and bilirubin levels.

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