

# Rectal indomethacin or intravenous gabexate mesylate as prophylaxis for acute pancreatitis post-endoscopic retrograde cholangiopancreatography

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**Abstract. – OBJECTIVE:** We aimed to evaluate the results in our case series of AP ERCP over the last three years. The prophylaxis for acute pancreatitis (AP) post-endoscopic retrograde cholangiopancreatography (ERCP) consists of rectal indomethacin, but some studies are not concordant.

**PATIENTS AND METHODS:** We compared 241 ERCP performed from January 2014 to February 2015 with intravenous gabexate mesylate (Group A), with the 387 ERCP performed from March 2015 to December 2016 with rectal indomethacin (Group B) as prophylaxis for AP post-ERCP.

**RESULTS:** There were 8 (3.31%) AP post-ERCP in Group A vs. 4 (1.03%) in Group B.

**CONCLUSIONS:** Rectal indomethacin shows a better statistically significant performance than intravenous gabexate mesylate in the prophylaxis of AP post-ERCP, besides being cheaper.

Key Words:

Post-ERCP acute pancreatitis, Indomethacin, Gabexate mesylate.

## Introduction

Acute pancreatitis (AP) is defined as a new upper abdominal pain, with increased serum amylase and/or lipase levels to at least three times above the normal limit<sup>1</sup>. This acute inflammation frequently involves peripancreatic tissues and, sometimes, remote organ systems. According to the Atlanta classification<sup>1</sup> forms, vary widely from mild, only affecting the pancreas, to severe disease with multi-organ failure and death. Mortality is higher in case of necrotizing pancreatitis (17%) than interstitial pancreatitis (3%). In cases of infected necrosis the mortality rate is 30%. The most frequent

mechanisms of AP are obstruction of the common bile duct by stones, and alcohol abuse. Endoscopic retrograde cholangiopancreatography (ERCP) is the most frequent iatrogenic cause. Post-ERCP AP is the most common and fear some adverse event for this procedure. In the United States this complication costs \$150 million annually for American Healthcare<sup>2,3</sup> and it is a common cause of endoscopy-related lawsuits against gastroenterologists in the world. It has a significant morbidity and rare mortality rate. About 10% of post-ERCP AP is moderate or severe. Post-ERCP severe AP is associated with a higher mortality than non-ERCP-induced pancreatitis, but without statistical evidence<sup>4</sup>. Post-ERCP AP has a prevalence of 5%, which is 2% in patients at low risk. More than 35 drugs have been studied for the prophylaxis of post-ERCP AP. Nowadays, indomethacin seems to be the best, but gabexate mesylate was used for many years<sup>5,6</sup>. Non-steroidal anti-inflammatory drugs (NSAIDs) are also known to have a protective action<sup>7-9</sup>. They are potent inhibitors of phospholipase A 2, cyclooxygenase, and neutrophil-endothelial interactions. All these inhibitors are believed to play an important role in the pathogenesis of AP, and NSAIDs seem to provide an increased benefit over temporary pancreatic stents, the only proven prophylactic intervention for post-ERCP AP<sup>10-12</sup>. Besides, NSAIDs are cheap and easily administered; when given as a single dose, they have a low risk. Many works<sup>13,14</sup> have reported the utility of rectal indomethacin as prophylaxis for post-ERCP AP. We investigated the number of AP post-ERCP that occurred using intravenous gabexate mesylate as prophylaxis in our hospitalized patients, from January 2014 to February

2015 vs. rectal indomethacin occurred from March 2015, when the clinical evidence became overwhelming for the use of this NSAID, until December 2016.

## Patients and Methods

Retrospectively, we analyzed 241 ERCP performed from the 1<sup>st</sup> of January 2014 to 28<sup>th</sup> February 2015 using gabexate mesylate (Istituto Biochimico Giovanni Lorenzini, Aprilia, LT, Italy), (1000 mg intravenously in 500 cc of saline solution during 24 h before ERCP) as prophylaxis for AP (Group A), compared to 387 ERCP utilizing rectal indomethacin (a suppository of 100 mg, Sigma-Tau Industrie Farmaceutiche Riunite, Pomezia, Rome, Italy), (1 h before ERCP) (Group B) from the 1<sup>st</sup> March 2015 to 6<sup>th</sup> December 2016 when this work was started. In Group A there were 110 men, 131 women, mean age 74 years (range 23-98 years). In Group B, there were 196 men and 191 women, mean age 74 years (range 33-96 years). The indications for ERCP, the complications and comorbidities of patients in Group A and Group B, were shown in Tables I-II.

## Statistical Analysis

The test for proportions of differences was used. Statistical significance of the differences between the two proportions (3.32% vs. 1.03%) was  $p = 0.042$ . When testing the null hypothesis of no association, the level of probability of error, two tailed, was 0.05. All the statistical

computations were made using Stata 10.0, Statistical Software (StataCorp 2007, College Station, TX, USA).

## Results

In Group A, there were 8 cases of AP (3.31%) and in Group B 4 cases (1.03%) (Figure 1). Between the two groups no differences in terms of major risk factors were found: precut sphincterotomy except 1 (Group B) patient, clinical suspicion of sphincter of Oddi dysfunction, a history of post-ERCP AP, pancreatic sphincterotomy, more than 8 cannulation attempts, pneumatic dilatation of an intact biliary sphincter except 1 (Group A) patient, ampullectomy<sup>15</sup>, or minor risk factors: female sex, age less than 50 years, history of recurrent pancreatitis, 3 or more injections of contrast agent into the pancreatic duct resulting in opacification of pancreatic acini, brushing of the pancreatic duct, minor operator experience. The duodenoscope used was always the same: Olympus TJFQ180V (Tokyo, Japan). None of our 12 patients with post-ERCP AP had active pancreatitis before ERCP, creatinine level > 1.4 mg, and no one was already taking NSAIDs (other than cardio protective aspirin). In six patients in Group A (Table III), ERCP was performed for choledocic lithiasis, in one for cholangiocarcinoma of the biliary tree (placement of prosthesis) and in one to change an occluded prosthesis (placed four months before for cholangiocarcinoma). Cholangitis was observed in

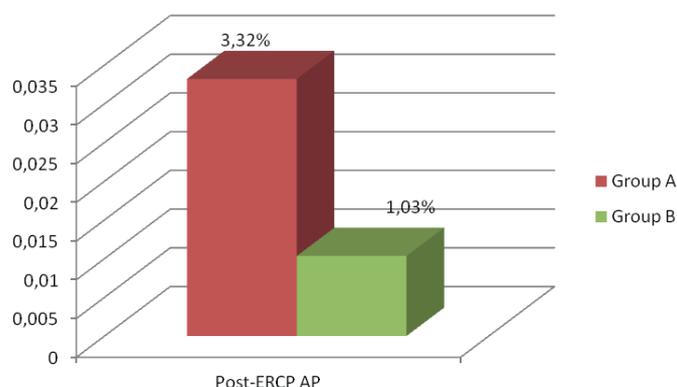


Figure 1. Percentual of cases of post-ERCP AP in Group A and Group B.

**Table I.** Characteristics of patients of Group A

<b>Comorbidities</b>	<b>%</b>	<b>Indication for ERCP</b>	<b>%</b>	<b>Complications in number of cases</b>	<b>Exitus in complications: number of cases</b>
Arterial hypertension	30	Choledocic lithiasis in previous cholecistectomy	24	Post-ERCP acute pancreatitis 8	0
Diabetes mellitus	13	Choledocic and cholelithiasis	21	Duodenal perforation 4	1
Ischemic cardiopathy	9	Cholangitis in choledocic lithiasis and previous cholecystectomy	16	Hematobilia 2	0
COPD	8	Biliary acute pancreatitis	10		
Chronic liver disease	5	Cholangiocarcinoma	7		
Atrial fibrillation	6	Choledocic stenosis for pancreas carcinoma	8		
Pace-maker	4	Stenosis of previous sphincterotomy	5		
Obesity	3	Sepsis in choledocic lithiasis in previous cholecystectomy	3		
Surrenal adenomas	2	Sepsis for occluded biliary prothesis in cholangiocarcinoma (the prothesis was changed)	3		
Liver metastasis	2	Biliary leakage after cholecystectomy	1		
Dyslipidemia	2	Primary sclerosing cholangitis	1		
Aortic valve prothesis	2	Choledocic stenosis by liver hilar linfoadenopathy in colon carcinoma	1		
Hyperthyroidism	2				
Pleural effusion	2				
Aortic insufficiency	2				
Ascites	2				
Pneumectomy for lung cancer	1				
Spontaneous bacteric peritonitis	1				
Carotid ateroma	1				
Aortic aneurysm	1				
Hiatal hernia	1				
Primary sclerosing cholangitis	1				
IPMT of pancreas	1				
Crohn's disease	1				
Lung metastasis	1				
Hypothyroidism	1				
Chronic kidney failure	1				
Alzheimer' disease	1				
Beta thalassemia	1				
Depression	1				
Parkinson's disease	1				
Inactive carrier of HBV	1				
Kaposi's sarcoma	0.2				

three patients and one had sepsis. One patient had hematobilia. No deaths occurred. In Group B (Table IV), in all four patients the ERCP was necessary for choledocic lithiasis. Two patients had cholangitis, one hematobilia and one hematobilia with duodenal perforation. This patient was treated not with surgical operation but with medical therapy. No deaths occurred. It is important to underline the considerable sum saved with the use of rectal indomethacin. In

fact, the cost of 10 vials of gabexate mesylate is 171.2 Euro and that of 500 ml of saline solution is 1.5 euro, for a total cost of 172.7 euro for every patient in Group A. A suppository of 100 mg of indomethacin costs 7.7 Euro, thus saving 165 Euro for each patient in Group B. Thus, for the 387 (Group B) patients the total saving was 63.855 euro in 21 months (Figure 2). Also, we saved about ten days of hospital treatment to each patient protected from post-ERCP AP

**Table II.** Characteristics of patients of Group B.

Comorbidities	%	Indication for ERCP	%	Complications in number of cases	Exitus in complications: number of cases
Arterial hypertension	32	Choledocic lithiasis in previous cholecystectomy	25	Hemato-bilia 4	0
Diabetes mellitus	14	Choledocic and cholelithiasis	20	Post-ERCP pancreatitis 3	0
Ischemic cardiopathy	9	Cholangitis in choledocic lithiasis and previous cholecystectomy	17	Duodenal perforation+ Hemato-bilia+ acute pancreatitis 1	0
COPD	8	Biliary acute pancreatitis	9	Duodenal perforation 1	1
Chronic liver disease	6	Cholangiocarcinoma	7		
Atrial fibrillation	6	Choledocic stenosis for pancreas carcinoma	8		
Pace-maker	3	Stenosis of previous sphincterotomy	4		
Obesity	3	Sepsis in choledocic lithiasis in previous cholecystectomy	4		
Surrenal adenomas	2	Sepsis for occluded biliary prothesis in cholangiocarcinoma (the prothesis was changed)	3		
Liver metastasis	2	Biliary leakage after cholecystectomy	1.5		
Dyslipidemia	2	Primary sclerosing cholangitis	1		
Aortic valve prothesis	2	Choledocic stenosis by liver hilar linfoadenopathy in colon carcinoma	0.5		
Hyperthyroidism	2				
Pleural effusion	2				
Aortic insufficiency	2				
Ascites	2				
Pneumectomy for lung cancer	1				
Spontaneous bacteric peritonitis	1				
Carotid ateromasia	1				
Aortic aneurysm	1				
Hiatal hernia	1				
Primary sclerosing cholangitis	1				
IPMT of pancreas	1				
Crohn's disease	1				
Lung metastasis	1				
Hypothyroidism	1				
Chronic kidney failure	1				
Alzheimer' disease	1				
Beta thalassemia	1				
Depression	1				
Parkinson's disease	1				
Inactive carrier of HBV	1				
Dilated cardiomyopathy	1				
Prostatic hypertrophy	1				
Pancreas divisum	1				
Mirizzi's syndrome	0.2				
Prostatic carcinoma	0,2				

with prophylactic rectal indomethacin: one day of hospital treatment costs about 1,500 euros, so for each patient we saved 15000 euros. Moreover, we have calculated as about 10 min the

time necessary to prepare 500 cc of saline solution with 10 vials of gabexate mesylate, whereas few seconds are necessary to prepare an indomethacin suppository.

**Table III.** Group A: Characteristics of the patients with AP post-ERCP.

Case	Name	Sex	Age	Reason of ERCP	Other complications	Risk factor	Other disease
1	L.M.S.	F	76	Choledocic lithiasis	None	None	Previous cholecystectomy for lithiasis
2	D.M.	F	81	Cholangitis In choledocic lithiasis	None	Pneumatic dilatation of biliary sphincther	Idem
3	R.M.	M	72	Cholangitis for occluded biliary prothesis in cholangiocarcinoma (the prothesis was changed)	None	None	Previous pneumectomy for lung carcinoma
4	C.A.V.	F	69	Choledocic lithiasis	None	None	Cholelithiasis, arterial hypertension
5	B.L.	M	63	Idem	None	None	Ischemic cardiopathy
6	E.A.	F	65	Idem	None	None	Cholelithiasis, diabetes mellitus
7	S.V.	F	89	Idem with cholangitis and sepsis	Hematobilia	None	Cholelithiasis, atrial fibrillation
8	D.C.	F	87	Cholangiocarcinoma (a biliary prothesis was placed)	None	None	Cholelithiasis, Kaposi's sarcoma



**Figure 2.** Cost of each patient of Group A and Group B.

### Discussion

This work confirms that the most common indication for ERCP is choledocic lithiasis (about 60%). In our case load post-ERCP AP was pre-

valent in females. Prophylaxis with rectal indomethacin is statistically significantly better than with intravenous gabexate mesylate. One dose of rectal indomethacin given immediately before ERCP reduced the prevalence of post-ERCP

**Table IV.** Group B: Characteristics of the patients with AP post ERCP.

Case	Name	Sex	Age	Reason of ERCP	Other complications	Risk Factor	Other disease
1	T.A.	F	62	Cholangitis in choledocic lithiasis	Hemato-bilia	Precut sphincterotomy	Pleural effusion
2	D.V.	F	77	Choledocic lithiasis	None	None	Arterial hypertension
3	C.V.	F	80	Cholangitis in choledocic lithiasis	None	None	Cholelithiasis, arterial hypertension, pancreas divisum
4	M.G.	M	50	Choledocic lithiasis	Duodenal perforation and hemato-bilia	None	Cholelithiasis, pleural effusion

AP. Previously published data suggested the use of rectal indomethacin immediately after ERCP. As in other works<sup>16</sup>, there was no significant difference between the two groups in the severity of bleeding events: no patients died. Nevertheless, in Group B there were 5 cases of hemato-bilia (1.3%), vs. 2 (0.8%) in Group A, without statistical significance. In the two groups the length of hospital stay was about the same for each patient. Because each patient with post-ERCP AP had to stay in hospital 10 days longer, we saved 40 days of hospitalization in Group B (about 60,000 euros). About risk factors, precut sphincterotomy was performed in one (Group B) patient and pneumatic dilatation of an intact biliary sphincter in one (Group A) patient; it is not possible to draw conclusions on this point. All the 12 post-ERCP AP were mild, no patient developed severe pancreatitis; instead, in literature about 10% of cases suffer pancreatitis<sup>4,17,18</sup>. Other studies showed a lower rate of severe pancreatitis in patients with gallstone disease and pancreas divisum<sup>4,19,20</sup>. We had one patient (Group B) with these characteristics and she had mild pancreatitis, but again no conclusions can be drawn on this point. Recently, many reports<sup>20-23</sup> have suggested that the use of lactated Ringer's solution before ERCP, with or without rectal indomethacin, is more effective than rectal indomethacin alone and than normal saline with or without indomethacin. The purported mechanism for the advantage of lactated Ringer's solution over normal saline is diminished pancreatic tissue acidification, thereby inhibiting zymogen activation and maintaining pancreatic microcirculation<sup>24</sup>. Nevertheless, other studies are necessary to confirm this point.

## Conclusions

Even if retrospective, our paper confirms that at the moment rectal indomethacin is the best prophylaxis for AP post-ERCP, as well as being much cheaper, and less time-consuming to administer than gabexate mesylate.

## Conflict of interest

The authors declare no conflicts of interest.

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