

Determining Frequency of Hyperamylasemia and Pancreatitis in Patients after Endoscopic Retrograde Cholangiopancreatography

Fabián Rodrigo Del Castillo Rangel¹, Lázaro Antonio Arango Molano²

¹ Resident in Clinical and Surgical Gastroenterology at the University of Caldas in Manizales, Caldas, Colombia. Email: fabiandelcastillo@hotmail.com
² Clinical and Surgical Gastroenterologist, Member of the Union of Surgeons SAS, Coordinator of the Surgical and Clinical Gastroenterology Program at the University of Caldas in Manizales, Caldas, Colombia. Email: lazaro.arango.m@gmail.com

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Abstract

We have seen with concern that there is confusion regarding the appearance of pancreatitis and the transient elevation of amylases (hyperamylasemia without clinical repercussions) in the postoperative period following ERCP (endoscopic retrograde cholangiopancreatography). For this reason, we embarked on the task of determining the prevalence of increased serum amylases and pancreatitis in patients who have undergone endoscopic retrograde cholangiopancreatography according to demographic, clinical and procedural variables. This is a descriptive, prospective, analytical and observational study. The study population consisted of 98 patients treated in the Union of SAS Surgeons who required endoscopic retrograde cholangiopancreatography.

Results: Acute pancreatitis was found in 2% of the patients who had undergone ERCP (Two of the 98 cases studied). Thirty patients (30%) presented hyperamylasemia. Cannulation of the pancreatic was associated with post-ERCP pancreatitis ($p < 0.05$). Pancreatic duct contrast had been used in one of the two patients who presented post-ERCP pancreatitis. Balloon dilation was associated with hyperamylasemia ($p < 0.041$).

Conclusions: Post-ERCP pancreatitis was found in two patients (2%), both of whom also presented hyperamylasemia which is one of the criteria for diagnosis of pancreatitis. The rate in our group is at the lower end of the international range of averages from 1.8% to 7.2%. Asymptomatic hyperamylasemia was present in 30% of our group. Following ERCP, we recommend that there is no need to measure amylases in patients who do not present pain. Amylase levels will be elevated in a large number of cases and will only cause confusion.

Keywords

Endoscopic retrograde cholangiopancreatography, ERCP, choledocholithiasis, pancreatitis, hyperamylasemia, pancreatic duct.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a relatively new procedure in our environment. Diagnosis and treatment of various benign or malignant pathologies of pancreatobiliary origin can be done with ERCP. Among the most frequent applications are diagnosis and treatment of bile duct and pancreatic duct calculi (choledocholithiasis), biliary stenosis of benign or malignant origin, stent placement for temporary or palliative relief of jaundice and

its possible complications, drainage of cholangitis, study and sampling of the bile duct, and palliative management of periampullary tumors (tumors of the head of the pancreas, the duodenum, the distal bile duct and the ampulla of Vater). ERCP also has the advantage of being less invasive for the patient, as there is no need to make incisions into the abdominal wall. This allows for faster patient recovery and earlier return to daily life. In addition, ERCP can be done under sedation in a short time either in the operating room or in an endoscopy room. The risk of post-ERCP pancrea-

titis “is higher among women, but these findings are confused by the presence of Oddi sphincter dysfunction which occurs more frequently in women.” (1)

Because the use of ERCP has increased in medium and high complexity institutions, complications such as pancreatitis, digestive bleeding, and digestive perforations have also become more evident. Other complications such as air embolisms, biliary lesions, fever and sepsis occur most frequently when this procedure is used for therapeutic purposes. Understanding the relative contribution and interactive effect of the multiple risk factors, a combination that progressively increases risk, can also be difficult. According to one study, “the risk of post-ERCP pancreatitis (PEP) increased from 5% in women with normal bilirubin levels to 16% adding to the difficulty of cannulation and suspected Oddi sphincter dysfunction (DEO), which elevates the risk up to 42%.” (2)

Asymptomatic pancreatitis and hyperamylasemia are frequently associated with ERCP. Asymptomatic pancreatitis is a very serious entity, while hyperamylasemia has a minimal statistical weight, with a reported incidence of around 50%. “Aggressive hydration decreases the systemic inflammatory response syndrome (SIRS), severity and complications in experimental and clinical studies. Measuring amylases or lipases four to six hours after ERCP can predict the development of PEP and help decide which patient should be hospitalized or discharged on the same day.” (3)

The most common complication of ERCP is pancreatitis, but it is often overdiagnosed. It has an incidence that ranges from 1.8% to 7.2% in most prospective series. The criteria defined for diagnosis have been accepted since 1991 and include abdominal pain of the pancreatic type associated with amylase or lipase levels at least three times their reference values. In addition, these two factors must occur within the first 24 hours after ERCP. Post-ERCP pancreatitis is one of the most common and feared adverse events related to ERCP which, “...results in considerable morbidity and, rarely, in death. The reported rate of post-ERCP pancreatitis varies from 1% to 40%, with an average of 5% to 7% that has been observed in retrospective and observational studies.”(4, 5)

Pain and symptoms need to be severe enough to require admission to the hospital or prolongation of a hospital stay. Although 80% of episodes of post-ERCP pancreatitis are mild, some patients develop severe pancreatitis and require prolonged hospitalization in the intensive care unit and the use of a greater amount of hospital resources. Physicians and patients should bear in mind that not all pain following ERCP constitutes post-ERCP pancreatitis. Also, transient hyperamylasemia without acute pancreatitis is common after ERCP. “Post-ERCP pancreatitis is defined as new

or increased abdominal pain that clinically corresponds to acute pancreatitis with typical pain in the epigastrium, radiating to the back and associated with elevation of serum amylase more than 3 times normal for more than 24 hours following ERCP and requiring hospital admission or prolongation of hospitalization.” (6)

Patient associated risk factors have been linked to high rates of post-ERCP pancreatitis in multivariate analyses. “Young age (younger than 60 years), female gender, history of post-ERCP pancreatitis, lack of dilation of the ducts, normal bilirubin level and suspicion of Oddi sphincter dysfunction are included. Likewise, chronic pancreatitis, particularly chronic calcified pancreatitis and pancreatic malignancy, have been shown to have a protective effect against post-ERCP pancreatitis. This is apparently due to decreased exocrine enzymatic activity and atrophy of the pancreatic parenchyma. Pancreas divisum, periampullary diverticulum, Billroth II gastrectomy, allergy to contrast medium and biliary interventions in patients with previous sphincterotomies are not associated with increased risk of post-ERCP pancreatitis.” (1, 7)

Although endoscopic retrograde cholangiopancreatography is a very effective procedure, it is also invasive which means it has potential complications including acute pancreatitis which can be very severe. Elevated levels of amylase enzymes without acute pancreatitis also occurs frequently as a consequence of the procedure. However, this is not a complication but rather a phenomenon related to the procedure. Hyperamylasemia of more than three times the normal range serum level of amylase plus pain typical of pancreatitis that persist for more than 24 hours constitutes acute pancreatitis. Hyperamylasemia alone with only elevation of enzymes in blood corroborated by laboratory results but without any additional clinical evidence can occur as part of the normal regular postoperative adjustment of the patient. Training of endoscopists depends on volume and experience. “It has been suggested that, independently, it contributes to the risk of PEP, but it has been difficult to evaluate, and training has been shown as a factor that increases the risk of PEP (OR 1.5, 95% CI: 1.029 -2.057, p = 0.03). Presumably, this is the result of a traumatic cannulation, the prolongation of a difficult cannulation or the excess in the use of electrocauterization during sphincterotomy.” (8)

Balloon dilatation of an intact biliary sphincter, “...has been associated with markedly increased risk of post-ERCP pancreatitis.” (9, 10) The use of pancreatic stents, “...has shown a reduction in the incidence and severity of PEP. The mechanism is to facilitate the drainage of the pancreatic duct by relieving the hypertension that develops as a result of the transient stenosis induced during the procedure.” (11)

MATERIALS AND METHODS

This is a descriptive, prospective, analytical and observational study (Table 1). The study population consisted of patients who had pancreatobiliary pathologies and who underwent ERCP in the Clinical-Surgical Gastroenterology Group of the Union of Surgeons SAS between July and September 2016. The selection and size of the sample responded to the evaluation of the clinical history. Patients who underwent ERCP for any reason, who were followed-up, and who signed informed consent for the required interventions were included. We excluded patients who presented complications, such as perforations, as well as those who underwent radical changes such as open surgical procedures.

Table 1. Distribution according to diagnosis

Diagnosis	Frequency	%	Accumulated
Choledocholithiasis with cholecystitis	3	3.1%	3.1%
Choledocholithiasis without cholangitis	60	61.2%	64.3%
Choledocholithiasis with cholangitis	1	1.0%	65.3%
Gall bladder cancer	1	1.0%	66.3%
Cholangitis	4	4.1%	70.4%
Cholelithiasis	3	3.1%	73.5%
Benign bile duct stenosis	13	13.3%	86.7%
Malignant bile duct stenosis	9	9.2%	95.9%
Biliary fistula	4	4.1%	100.0%
Total	98	100.0%	

RESULTS

In total, the study included 98 patients who required ERCP. The incidence of post-ERCP pancreatitis was 2%: one patient had mild pancreatitis, and another had severe pancreatitis for a total of two patients with post-ERCP pancreatitis throughout the study. Of the 96 remaining patients, none developed this condition (98%). The incidence of hyperamylasemia was 30% (30 patients). Twenty-eight of these patients with elevated levels of amylases did not have pancreatitis. The two patients who developed pancreatitis also had elevated levels of amylases. Women were the majority of patients: 52 patients which corresponded to 53%. The municipality of origin Manizales accounted for 76% of the patients. The most frequent diagnosis was choledocholithiasis without cholangitis which was found in 59 patients (60.2%) (Tables 2, 3 and 4).

The pancreatic duct was cannulated in only nine patients (9%), but there was a statistical association between cases of pancreatitis and cannulation of the pancreatic duct, with

a value of $p < 0.05$ (Table 5). The two patients who had pancreatitis were cannulated. Contrast medium was used in the pancreatic ducts of six patients (6%) including in one of the two patients who developed pancreatitis. Contrast medium was not used in the other 92 patients (94%). Although 50% of the cases of pancreatitis are included in the subset of those who received contrast medium, we estimate that there is no valid statistical association due to the small number of cases. Nevertheless, if we give importance to the half of the cases of patients who underwent balloon dilation, there is a positive statistical association for patients who presented hyperamylasemia ($p < 0.041$) (Table 6).

Table 2. Distribution according to pancreatitis

Pancreatitis	Frequency	%	Accumulated
Without pancreatitis	96	98.0%	98.0%
Mild	1	1.0%	99.0%
Severe	1	1.0%	100.0%
Total	98	100.0%	

Table 3. Distribution according to sex

Sex	Frequency	%	Accumulated
Male	46	47.0%	47.0%
Female	52	53.0%	100.0%
Total	98	100.0%	

Table 4. Distribution according to hyperamylasemia

Hyperamylasemia	Frequency	Percentage
With hyperamylasemia	30	30.6%
Without hyperamylasemia	68	69.3%
Total	98	100%

Only seven patients underwent balloon dilation while the other 91 patients did not (Table 7). Neither of the patients who developed acute pancreatitis underwent balloon dilation, but we must emphasize that balloon dilation it is not a routine procedure nor is it favored by our group due to the associated risk of pancreatitis. The small number of cases analyzed prevents calculation of a relevant statistical relationship. Twenty-one patients (21%) had precut papillotomies while 77 did not. In total, 53 patients (54%) had papillotomies, but 45 (46%) did not. No statistical association was demonstrated for pancreatitis or hyperamylasemia.

The reasons for performing ERCP included choledocholithiasis without cholangitis (60 patients, 61.2%), benign stenoses of the bile duct (13 patients, 13.2%), malignant stenoses of the bile duct (9 patients, 9.2%), biliary fistulas

Table 5. Distribution according to pancreatitis and cannulation of the pancreatic duct

Cross-referenced Table					
			Cannulation of the pancreatic duct		Total
			Yes	No	
Presence of pancreatitis	Yes	Count	2	0	2
		% with pancreatitis	100.0%	0.0%	100.0%
		% who underwent cannulation of the pancreatic duct	22.2%	0.0%	2.0%
	No	Count	7	89	96
		% with pancreatitis	7.3%	92.7%	100.0%
		% who underwent cannulation of the pancreatic duct	77.8%	100.0%	98.0%
Total	Count	9	89	98	
	% with pancreatitis	9.2%	90.8%	100.0%	
	% who underwent cannulation of the pancreatic duct	100.0%	100.0%	100.0%	
Chi squared test					
	Value	df	Asymptotic significance (2 tailed)	Exact significance (2 tailed)	Exact significance (1 tailed)
Pearson's Chi squared test	20.190 ^a	1	0.000		
Continuity correction ^b	10.604	1	0.001		
Likelihood ratio	9.991	1	0.002		
Fisher's exact test				0.008	0.008
Linear by linear association	19.984	1	0.000		
No. of valid cases	98				

a. Two boxes (50.0%) have expected counts of less than 5. The expected minimum count is 18.

b. This has only been calculated for a 2 x 2 table.

(4 patients, 4.1%), choledocholithiasis with cholecystitis (3 patients, 3.1%), and choledocholithiasis with cholelithiasis (3 patients, 3.1%). One patient (1.0%) had choledocholithiasis, another one (1.0%) had choledocholithiasis with cholangitis, and another one (1.0%) had gallbladder cancer.

DISCUSSION

Our work shows that post-ERCP pancreatitis occurred in 2% of our target group was 2%. Although it is relatively frequent, this finding suggests that, in experienced hands of physicians with high levels of training, it should be diagnosed less frequently than it currently is. Asymptomatic hyperamylasemia without clinical implications for the patient occurs quite frequently (30%). We recommend that amylase levels of patients who do experience pain following ERCP should not be measured. These levels will be elevated in a large number of cases, and this might cause confusion.

Cannulation of the pancreatic duct and post-ERCP pancreatitis had a statistically significant association, with $p < 0.05$. This association existed in both cases in which the condition occurred.

There was no statistical association between the use of contrast in the pancreatic duct and post-ERCP pancreatitis although contrast was used in one of the two cases of acute pancreatitis. However, since this is 50% of the cases which developed acute pancreatitis, we do attach importance to this fact. Balloon dilation of the papilla also showed a statistically significant association with elevation of amylases, although it was not statistically related to pancreatitis. This could be due to the fact that it is not routinely used in our group due to the high risk of post-ERCP pancreatitis, and also due to the small number of cases in the sample. Twenty-one patients (21%) underwent precutting prior to papillotomies while 75 (78%) did not. Neither of the patients who developed pancreatitis underwent pre-

Table 6. Distribution according to pancreatitis and use of contrast in the pancreatic duct

Cross-referenced Table					
		Contrast Used In Pancreatic Duct		Total	
		Yes	No		
Presence of pancreatitis	Yes	Count	1	1	2
		% with pancreatitis	50.0%	50.0%	100.0%
	No	% with contrast in pancreatic duct	16.7%	1.1%	2.0%
		Count	5	91	96
	Total	% with pancreatitis	5.2%	94.8%	100.0%
		% with contrast in pancreatic duct	83.3%	98.9%	98.0%
		Count	6	92	98
		% with pancreatitis	6.1%	93.9%	100.0%
		% with contrast in pancreatic duct	100.0%	100.0%	100.0%

Chi squared test					
	Value	Gl	Asymptotic significance (2 tailed)	Exact significance (2 tailed)	Exact significance (1 tailed)
Pearson's Chi squared test	6.839 ^a	1	0.009		
Continuity correction ^b	1.266	1	0.251		
Likelihood ratio	3.087	1	0.079		
Fisher's exact test				0.119	0.119
Linear by linear association	6.769	1	0.009		
No. of valid cases	98				

a. Two boxes (50.0%) have expected counts of less than 5. The expected minimum count is 12.

b. This has only been calculated for a 2 x 2 table.

Table 7. Distribution according amylase level and ranges of dilatation of the papilla.

Ranges				
	Dilation of the papilla	N.º	Average Range	Sum of ranges
Amylase level	Yes	7	70.64	494.50
	No	91	47.87	4356.50
	Total	98		

Statistical Tests ^a	
	Amylase level
Mann-Whitney U	170.500
Wilcoxon signed-rank test	4356.500
Z-test	-2.043
Asymptotic significance (bilateral)	0.041

cutting. There were no statistically significant associations between performance of routine papillotomy and either hyperamylasemia or acute pancreatitis.

There is evidence suggesting that early precutting after 5 to 10 cannulation attempts may decrease the risk of PEP below that which occurs following persistent attempts

at cannulation which traumatizes the papilla. Two meta-analyses that included six randomized controlled trials which compared early pre-cutting with multiple attempts at cannulation using a standard approach have shown significant reductions of PEP (OR 0.47, 95% CI: 0.24-0.91). In addition, it was possible to demonstrate that precutting

also reduced the time required to perform ERCP which could be beneficial for elderly patients and those have high levels of ASA.

CONCLUSIONS

We consider that cannulation, use of contrast in pancreatic ducts and dilation of the papilla are potential risk for acute pancreatitis that can be modified. Performance of early pre-cut before a difficult cannulation may be a protective factor which can be modified as long as the ERCP is performed by a trained professional.

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